

**An Assessment of Genetic Counselors' Knowledge and Attitudes  
Regarding Gene Transfer Therapies**

by

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**Abstract**

**Background:** There are currently two FDA approved gene transfer therapies, Luxturna (voretigene neparvovec-rzyl) to treat *RPE65* Associated Inherited Retinal Dystrophy and Zolgensma (onasemnogene abeparvovec-xioi) to treat Spinal Muscular Atrophy. No practice guidelines or educational tools designed for genetic counselors exist regarding gene therapies. Research demonstrates that the majority of healthcare providers lack knowledge regarding gene therapies. The comfort level of genetic counselors and their impact on genetic counseling sessions has not been explored. This study aims to identify any knowledge gaps in practicing genetic counselors and to investigate educational resources. This information will become more broadly applicable over time.

**Methods:** An electronic survey of 22 questions was sent to genetic counselors. Multiple choice questions, open-ended questions, and Likert scales were used to explore the respondents' experiences and perceptions as they relate to the aims of this study.

**Results:** 109 genetic counselors responded to the survey. 54 participants worked in pediatrics, 38 in metabolic disorders, and 29 in prenatal and cancer each. 56% of participants had 5 years of experience or less. 5% and 28% of participants responded they “never heard of” Zolgensma and Luxturna, respectively. 10% and 20% of participants responded they were “not comfortable” with Zolgensma and Luxturna, respectively. Answers for these questions varied based on specialty and experience. Analysis showed that counselors in certain specialties were more likely to be familiar

with gene therapies and more likely to discuss them with patients, while counselors in specialties such as cancer were less likely to be familiar or to discuss gene therapies. 59% of participants felt that gene therapies impacted their work and 93% of participants felt that genetic counselors should be comfortable discussing gene therapies with patients. 83% of participants were interested in additional training in various formats, with seminars hosted by NSGC as the most common answer.

**Conclusions:** Genetic counselors felt that available gene therapies do impact their sessions. While respondents wanted to be involved in counseling patients regarding gene therapy, they desired additional training to be prepared to do so.

**Public Health Significance:** Additional education is needed for genetic counselors to counsel patients regarding gene transfer therapies.

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## 1.0 Introduction

“Gene therapy” is an umbrella term that can be divided into three different types of treatment: gene editing, cell therapy, and gene transfer. Gene editing is a process where DNA with genetic variants is cleaved and donor DNA is inserted. An example of gene editing is CRISPR/Cas9. Cell therapy is when cells are removed from a patient, treated *ex vivo*, and then re-injected into the patient. An example of this is CAR T-cell therapy that has been used to treat cancers. Gene transfer utilizes viral vectors to introduce functional copies of a gene into the body. This project focused the two gene transfer therapies that are currently approved by the FDA to treat genetic disorders. Luxturna (voretigene neparvovec-rzyl) is used to treat *RPE65* Mutation-Associated Retinal Dystrophy. Spinal Muscular Atrophy (SMA) can be treated with Zolgensma (onasemnogene abeparvovec-xioi).

There are currently no practice guidelines or educational tools regarding gene therapy treatments that are specifically designed for genetic counselors. While it is natural for genetic counselors to be involved in the care of patients who may benefit from these treatment methods, the comfort level of genetic counselors regarding gene transfer and the impact of these two treatments on genetic counseling sessions has not been explored. A study was recently published in an effort to identify the knowledge gaps that healthcare providers (doctors, nurses and physician assistants) had with regard to gene therapy. This study showed that “63% of survey respondents were unaware of current FDA approved gene therapies” (Rare Neurological Disease Special Report, 2020), which indicates that additional education is needed among these provider types. A separate survey was conducted to assess the practices and knowledge of prenatal genetic

counselors in regards to Spinraza (nusinersen), a cell therapy for SMA. It was reported that 73.6% of respondents “knew “a little bit” or “quite a bit”” about Spinraza (Zettler, 2019). However, only 12.1% of counselors felt comfortable discussing gene therapy with their patients (Zettler, 2019). Zettler et al. identified that additional education was needed for genetic counselors.

This current study assessed the following hypotheses:

- Genetic counselors who are not in specialty clinics with gene transfer therapy available (or with current or previous clinical trials) will report insufficient knowledge about gene transfer therapy.
- Genetic counselors who are unfamiliar with available gene transfer therapies will not feel able to properly educate patients on available treatments.
- Genetic counselors would appreciate additional training and education related to gene transfer, as they will be essential parts of healthcare teams providing gene transfer therapies to individuals with genetic disorders.

The specific aims of this study were to:

- Conduct an electronic survey of genetic counselors to measure the knowledge and comfort level that genetic counselors have regarding gene transfer therapies.
- Assess if there are differences between the knowledge and comfort level of specific demographic groups of genetic counselors.
- Investigate how the availability of gene transfer therapies impacts a genetic counseling session.
- Describe how the findings of this study can be used to improve training of genetic counselors in the field.

This study aimed to identify any knowledge gaps in practicing genetic counselors, to assess if current training efforts are sufficient, and to investigate what educational resources can be utilized. This information will become more broadly applicable as more gene therapies are approved in the future.

## **2.0 Literature Review**

### **2.1 Types of Gene Therapies**

“Gene therapy” is an umbrella term that refers to multiple techniques that are used to correct, replace, or supplement non-functioning genes. Gene therapy can be used to treat genetic diseases such as monogenic disorders or cancer. Although there are many techniques that can be used for “gene therapy”, the goal is the same: to introduce a working copy of a gene into a patient to prevent or alleviate disease. This type of treatment can be further divided into categories: gene transfer, gene editing, and cell therapy. There are also multiple treatments for genetic conditions that address the genetic defect but are not technically gene therapies because they do not provide a copy of the functional gene.

Gene transfer therapy involves adding a functional copy of the target gene into the body. The functional gene product requires a vector for transmission into the patient’s cells, so this must be designed in a laboratory. Often, the vectors are viral. The functional gene product may integrate into the cells’ DNA, or it may replicate on its own. Viral vectors that integrate are effective in cells that frequently divide, because it allows the corrected gene to be present in future generations of cells (Explore Gene Therapy, 2020). Vectors that do not integrate are more effective in organs with cells that do not regenerate often, such as the brain or liver. One particular benefit of gene transfer therapies is that treatments can be injected directly into affected tissues. For example, Luxturna (voretigene neparvovec-rzyl) is injected into the subretinal space.

Possible vectors for gene transfer therapy include non-viral methods, retroviruses, or adenoviruses. Nonviral gene transfer therapy can be achieved using chemical methods such as calcium phosphate or utilizing liposomes or molecular conjugates (Lea, 1997). Cotrim and Baum describe nonviral vectors as “considered to be much safer than viral vectors, but ... fairly inefficient at transferring genes” (Cotrim & Baum, 2008). Viral vectors were used in approximately 70% of clinical trials prior to 2004 (Cotrim & Baum, 2008; Edelstein, Abedi, Wixon, & Edelstein, 2004). When human clinical trials began, the most common viral vectors that were used were the Moloney murine leukemia virus (MoMLV), which is a retrovirus, and a serotype 5 adenovirus (Ad5) (Cotrim & Baum, 2008). Now, the most common vectors are adeno-associated viruses (Venditti, 2021).

Retroviruses are a family of viruses that utilize RNA segments to integrate their genetic material into the DNA of rapidly dividing cells. The functional gene product will be produced by these cells and any future generations of these cells, which can show long term benefits. However, the RNA segment inserts randomly into the cells’ DNA. It is possible that the retrovirus can insert into a coding region and interfere with another gene’s function. In contrast, adenoviruses do not integrate into the host genome, and they are composed of DNA instead of RNA. Adenoviruses can infect numerous cells without needing the cells to replicate, so they are useful in specific cell types (Lea, 1997). However, this might require multiple treatments to be effective. It is also possible that a patient’s immune system could react to the adenovirus, rendering it ineffective. Adeno-associated viruses were initially discovered as a contaminant of adenovirus preparations, and consist of a protein shell and a small segment of DNA that cannot replicate on its own (Naso, Tomkowicz, Perry, & Strohl, 2017). When the viral DNA is removed, and only the protein shell remains, it is referred to as recombinant AAV (rAAV).

rAAVs do not integrate into the host genome and similar to adenoviruses, may require multiple treatments (Naso et al., 2017). This is the vector type used for the two currently FDA approved therapies.

Gene editing is used to replace or change someone's DNA at a specific location in order to correct pathogenic mutations and restore the gene's function. One example of this technique is called CRISPR, which stands for clustered regularly interspaced short palindromic repeats. CRISPR allows for "targeted modification of specific DNA sequences in the genomes of living cells" (Ormond et al., 2017). This treatment utilizes a CRISPR RNA sequence and a Cas9 protein target to cleave a certain DNA sequence, which causes a break, deletion, or mutation at that desired location. A donor fragment of DNA with a functional copy of the target gene can then be integrated by the host cell's own DNA repair machinery. This provides a technique for possibly curing single gene disorders, in somatic or germline cells. Although this has not been approved in human embryos, CRISPR technologies have been used to edit mouse zygotes (Ormond et al., 2017; Chen, 2016). However, this type of treatment has the potential for undesired cleavage or "edits" at the target DNA in the host cells and the technology is not yet as precise as desired. The ethical ramifications of this technique are being debated and currently there are no human trials approved by the FDA.

Cell therapy involves removing cells from a patient, treating those cells ex vivo, and then returning them to the patient's system. It is suggested that this could be used to treat autoimmune or neurologic disorders or for repairing cartilage or spinal cord injuries (Explore Gene Therapy, 2020). Cell therapy was used in the Rosenberg study of 1990 described below, where treated cells were meant to attack malignant melanoma cells. A similar example of cell therapy is chimeric antigen receptor (CAR) T-cell therapy, which is meant to treat cancer. CAR-T cell



involves removing a patient's T cells and adding genetic information to them *ex vivo*. The treated T cells are able to make specific receptors called chimeric antigen receptors. When the treated cells are injected back into the patients, they should be able to recognize and attack cancer cells.

There are also treatment methods that may be incorrectly considered "gene therapy." One example is antisense oligonucleotides (ASOs), which alter RNA and in turn modify protein expression (Rinaldi & Wood, 2018). ASOs have been approved to treat Duchenne Muscular Dystrophy and Spinal Muscular Atrophy. Mitochondrial replacement therapy, when a donor egg provides a functional copy of the mitochondrial genome, has been used in the United Kingdom to prevent mitochondrial disease. However, patients and some providers may not know that these are not technically gene therapies.

## **2.2 History of Gene Therapies**

The development of recombinant adeno-associated virus (rAAV) gene therapies has only been possible with the improved understanding of basic virology, the creation of genomic technologies, continuous research and economic investment in treatment of rare diseases. Adeno-associated virus (AAV) was initially discovered in the 1960s by Atchison et al. (Atchison, Casto, & Hammon, 1966). The Berns laboratory next proved that AAV infection was possible and that wild type adeno-associated viruses could integrate into human chromosomes (specifically, chromosome 19) (Berns, Pinkerton, Thomas, & Hoggan, 1975). The Berns group also detailed the mechanism of wild-type and recombinant AAV in the 1970s (Berns, Pinkerton, Thomas, & Hoggan, 1975).

It became apparent in the 1980s that AAV2 could be used as a means for gene transfer therapies. Samulski et al. published in 1989 that they were able to infect HeLa cells with rAAV preparations with minimal wild-type information (Samulski, Chang, & Shenk, 1989). The first time this technique was applied to human genetic disorders was an attempt to develop a vector for treatment of cystic fibrosis (Flotte et al., 1993). The Carter and Flotte laboratories, as well as the Targeted Genetics Corporation, attempted to develop a cystic fibrosis transmembrane conductance regulator called rAAV2-CFTR (Flotte et al., 1993). The treatment was developed to be used in the respiratory tracts of subjects with cystic fibrosis (Flotte et al., 1993). One challenge was the large size of the *CFTR* gene, which was estimated at 4,400 nucleotides (Flotte et al., 1993). Since the AAV limit for the target DNA was about 4.5 kilobases, this did not allow much room for a transcription promoter (Flotte et al., 1993). The Flotte group discovered that inverted terminal repeats (ITRs) containing instructions for replication, encapsulation, and integration acted as a promoter region (Flotte et al., 1993). The ITRs allowed the AAV to be an effective vector of an appropriate size (Flotte et al., 1993). However, these ITR sequences were homologous to the transcriptional start sites of many other genes, which meant that the vector might have caused overproduction of other proteins besides CFTR (Flotte et al., 1993).

In the 1990s and early 2000s, ways to improve the efficacy of adeno-associated viral treatments were discovered. One advancement was the understanding that treatment sites had an impact on how effective specific vectors were, a phenomenon known as tropism. For example, a study published in 2005 compared AAV1, AAV6, and AAV8 in various tissues in mice and hamsters. The AAV1 and AAV6 vectors were only expressed in skeletal muscle, while the AAV8 vector was expressed in skeletal muscle, cardiac cells, and liver cells (Wang et al., 2005). In neonatal mice, the AAV8 vector was retained in the heart and muscle cells and degraded in the

liver during cell growth and division (Wang et al., 2005). In adult mice with fully developed livers, and therefore less cell division, the AAV8 was retained in the liver as well as heart and skeletal muscle (Wang et al., 2005). This study also showed that the efficiency of such treatment was greater in neonatal mice (Wang et al., 2005). These discoveries were important for the development of human treatments.

Cotrim notes that the first gene transfer therapy clinical study in humans was reported in 1990 (Cotrim & Baum, 2008). The study examined the efficacy of using retroviral-mediated gene transduction in tumors from subjects with metastatic melanoma at the National Institutes of Health (Rosenberg, 1990). Retroviral vectors were used to transfer neomycin resistance genes into the lymphocytes of the subjects. The use of the neomycin resistance gene as a genetic marker was chosen because it was present in treated cells and all their progeny for as long as they survived, was non-transferable between cells, and the procedure was nontoxic to both healthy and tumorous cells (Rosenberg, 1990). In this study, the gene transfer products were modified leukocytes that had been removed from and reintroduced to the five subjects, a form of cell therapy.

Results were confirmed and measured with Southern Blots and PCR reactions. PCR analysis showed that the introduced genetic changes were still present in subject samples for up to three weeks in all five subjects (Rosenberg, 1990). Two subjects still had the gene products two months later, which showed the longevity of the treatment (Rosenberg, 1990). This treatment appeared to be safe for subjects as well. Rosenberg et al. did not note any side effects in these subjects that were not seen in subjects receiving standard tumor-infiltrating leukocytes (TIL) and interleukin-2 treatments (Rosenberg, 1990). Cautions were taken to ensure that the viral agent could not replicate independently (Rosenberg, 1990). The retrovirus was an altered form of the Moloney murine leukemia virus whose viral genes were modified so that RNA packaging could

not occur, and the virus could not “infect” the subject (Rosenberg, 1990). Additional testing showed that the virus was unable to replicate in the subjects (Rosenberg, 1990).

Theoretically, the vectors could have randomly inserted themselves into or near an oncogene in the host cells’ genome, resulting in malignant transformation of the TIL. Testing showed that transduced tumor-infiltrating leukocytes were not negatively affected (Rosenberg, 1990). It was also possible that the vector could have recombined in an endogenous sequence in the human genome, which may have allowed for the virus to replicate. There were no known homologous sequences to the vector, so this chance was described as “remote” (Rosenberg et al., 1990). The results of this study showed that retroviral gene transduction was feasible and safe. Rosenberg et al. suggested that this method could be applied to treat genetic disorders such as hemophilia or severe combined immunodeficiency (Rosenberg et al., 1990).

Severe combined immunodeficiency–X1 (SCID-X1) is inherited in an X-linked manner. Pathogenic mutations in the *IL2RG* gene negatively impact the production, growth, and survival of lymphocytes (U.S. National Library of Medicine, 2020). When lymphocytes are not correctly formed and differentiated, the immune system cannot develop properly or regulate itself (U.S. National Library of Medicine, 2020). This leads to recurrent infections in patients (mostly males) with this condition, and often individuals die in infancy without treatment (U.S. National Library of Medicine, 2020). A clinical trial to treat X-linked severe combined immunodeficiency (SCID-X1) began in 2000. The method of potential gene therapy targets for SCID-X1 was similar to Rosenberg’s treatment of melanoma subjects. T lymphocytes in SCID-X1 subjects were predicted to be an advantageous target for gene therapy because the cells were long-lived transduced cells, meaning that the gene expression would be also long lived (Cavazzana-Calvo et al., 2000). Another

advantage of this study was that subjects with SCID had no immune system, which meant that there was no chance of an immune reaction to the viral vector.

A gene therapy trial was performed on two infant subjects. The goal of this treatment was to use a Moloney retrovirus–derived vector to restore the function of T cells, B cells, and NK cells in order to correct the subjects’ immune systems (Cavazzana-Calvo et al., 2000). Cavazzana-Calvo used  $\gamma$ c gene as a target for transfer. It was predicted that the  $\gamma$ c gene would integrate into lymphoid progenitor cells and allow them to properly communicate with T and NK lymphocyte progenitors, and ultimately restore immune function (Cavazzana-Calvo et al., 2000). The first step was to harvest marrow from the two subjects and infect the sample for three days with “MFG  $\gamma$ c vector–containing supernatant” (Cavazzana-Calvo et al., 2000).  $\gamma$ c transgene expression was measured using PCR analysis or immunofluorescence (Cavazzana-Calvo et al., 2000). PCR analysis detected the  $\gamma$ c transgene in peripheral blood samples at day fifteen, and the fraction of “corrected” blood cells increased over time (Cavazzana-Calvo et al., 2000). T cell counts increased during this time frame as well. Southern blot analysis was used to show that “that multiple T cell precursors had been infected by the retroviral vector” (Cavazzana-Calvo et al., 2000).

Ten months after the initial treatment, the T, B, and NK cell counts and function in the subjects were comparable to control samples from unaffected individuals (Cavazzana-Calvo et al., 2000). Cavazzana-Calvo described the trial as a success and stated, “gene therapy was able to provide full correction of disease phenotype and, hence, clinical benefit” (Cavazzana-Calvo et al., 2000). Those two infants were able to leave the hospital and were considered cured (Cavazzana-Calvo et al., 2000). This trial proved that gene therapy could be effective in human subjects, and more trials were initiated based on this success.

When gene therapy was initially conceived, experts expected developments to come quickly and for progress to be rapid. However, progression of the technique was slower than initially predicted and did have some setbacks. In 1999, a participant in a gene therapy trial died four days after receiving gene therapy. Jessie Gelsinger was participating in a clinical trial at the University of Pennsylvania that utilized a modified Ad5 vector to deliver functional copies of the *ODC* gene to subjects with ornithine transcarbamylase deficiency. An investigation into his death found that Gelsinger had an immune reaction to the Ad5 vector that caused multiple organ failure and led to his death (Cotrim & Baum, 2008; Raper et al., 2003). The tragedy of Gelsinger's death drew extreme media attention to gene therapies. Public hearings regarding gene therapy clinical trials were held by the Food and Drug Administration (FDA) in response. The investigation revealed that Gelsinger should have been excluded from the trial based on his high ammonia levels (Wilson, 2009). The University also failed to disclose that two other subjects had serious side effects, and that monkeys that were previously given similar treatment had died (Wilson, 2009). Additional animal studies were performed after this event which showed that antigen-presenting cells (APCs) in the spleen and liver were targeted by the capsid of the vector (Raper, 2003). This meant that modifications made to the virus to reduce expression of the viral genes and limit immune response would not be effective (Raper, 2003). The FDA placed a temporary hold on all AAV clinical trials and it was determined that additional regulations would be needed for any future trials, under the supervision of the National Institutes of Health (NIH) and FDA (Cotrim & Baum, 2008).

Despite this, the potential benefits of gene therapies encouraged continued research even with increased regulation. As seen in 1999, utilizing viral vectors to transport genetic products could cause the subject's immune system to respond overwhelmingly. Immune and inflammatory

responses occur as natural reactions to foreign viruses, which makes identifying appropriate viral vectors a challenge. Another complexity is that the body's immune system may recognize the viral vector being used in a repeated therapy and respond accordingly, destroying the vector and target gene, and render the treatment useless (Mandal, 2019).

Since this is a relatively new treatment option, there is not information on any long-term effects. Gene therapies are ideally designed to be long-lasting and permanent, however, this can be challenging. Cells that divide rapidly may not pass on the functional gene product to their progeny and therefore, may require repetitive treatment (Mandal, 2019). While gene therapies were designed to insert in certain non-coding regions of the genome, it is possible that the introduced gene could be inserted into the wrong region. For example, a product inserted into a tumor suppressor in the subject's body could interrupt that gene's function and lead to tumor growth. This process, called insertional mutagenesis, has been well documented in retrovirus research in laboratory animals but not as well studied in humans (Bushman, 2020). Retroviruses could also unintentionally integrate into enhancer or promoter region and negatively impact a gene's function without altering the gene product. This was a concern noted by the Rosenberg study, although it didn't actually occur.

### **2.3 RPE65 Disorders and Luxturna**

Leber congenital amaurosis (LCA) is a collection of retinal dystrophies that are inherited in an autosomal recessive manner. Twenty genes are listed in Online Mendelian Inheritance in Man®, and pathogenic variants in these genes can cause the different types of LCA by negatively impacting the retina's function (Johns Hopkins University, 2021; Koenekoop, 2008).

The thirteen types of LCA can be differentiated by the mechanism of disease or the clinical symptoms that are seen. LCA is characterized by absent ERG (electroretinography) signals and the onset of blindness or vision loss at birth. Other common symptoms of LCA are sensitivity to light, nystagmus, extreme farsightedness, and abnormal pupillary reactions to light. A behavior that is often noticed as one of the first symptoms is called Franceschetti's oculo-digital sign, which is when patients rub or poke their eyes consistently. Although LCA is rare, about 200,000 individuals across the globe have some form of the disorder (Koenekoop, 2008). It is thought to be the most common cause of infant blindness (Koenekoop, 2008). Chao et al. estimates the incidence of LCA to be anywhere from 1/81,000 to 3/100,000 (Chao et al., 2019). One of the genes that can cause LCA is *RPE65*.

All causative variants in *RPE65* are thought to be loss-of-function changes that negatively impact the function of the RPE65 protein (Chao et al., 2019) and interrupt the vitamin A cycle in the eye. There are no established genotype-phenotype correlations that could be used to predict the severity of symptoms. With the exception of one family with a documented multi-exon deletion, all reported pathogenic *RPE65* variants are sequencing variants (Chao et al., 2019). Individuals with *RPE65* Associated LCA begin to show symptoms from birth to age five. Vision tends to be stable at first, then decline during adolescence, progress to legal blindness by age twenty (Chao et al., 2019), and then to decline further as the patient ages. While the vision impairment is severe, the retinal structure is preserved. Keonekoop describes the preservation as, “Retinal architecture is much better preserved in patients with RPE65 defects than would be expected based on their low visual function.” (Koenekoop, 2008). This meant that RPE65 mutations would be an ideal target for treatment and possible vision rescue, since there are still working rods and cones.



*RPE65* pathogenic variants have been associated with other eye disorders, including autosomal recessive retinitis pigmentosa type 20, early-onset severe retinal dystrophy (EOSRD), and autosomal dominant mild retinitis pigmentosa with a choroideremia phenotype. Symptoms of *RPE65* associated LCA can include myopia, nystagmus, poor pupillary light response, or poor night vision. Central vision is variable but sometimes preserved. Clinical examinations can be variable as well, and fundus exams may be normal. However, clinical findings include “RPE mottling, pigmentary retinopathy with attenuated vessels, optic nerve pallor, white spots at the level of the RPE, parafoveal RPE loss as a bull's eye maculopathy, and optic disc drusen” (Chao et al., 2019). One test that is used to assess how the rods and cones are functioning is an electroretinogram (ERG). ERG findings for patients with *RPE65* associated LCA are severely abnormal or undetectable (Chao et al., 2019). Individuals with *RPE65* associated LCA have normal intellect, but children may have behavioral issues or learning challenges because of their visual impairments. Previously, the only treatment for the condition was nutrient supplementation, a healthy diet with emphasis on omega-3 fatty acids, antioxidant-rich foods, and lutein-rich foods, and symptom management such as vision therapy or using a flashlight (Chao et al., 2019). Regular ophthalmologic evaluations are needed to assess the patients’ photoreceptor function over time. Other management tools that can be used include developmental or psychiatric evaluations. Patients can also utilize resources such as vision therapy or Individual Education Plans in schools.

In the early 2000s, two research groups began testing *RPE65* gene replacement therapies in humans. A research group in Philadelphia utilized an adeno-associated virus (AAV) called AAV2.hRPE65v2 with a chicken  $\beta$  actin (CBA) promoter (Maguire et al., 2008). Another research group in London utilized an AAV called AAV 2/2.hRPE65 with a human *RPE65*

promoter (Bainbridge et al., 2008). The Philadelphia group used a surfactant but the London group did not. Both studies included three patients who received treatment injected subretinally at what were considered low viral doses. No side effects or inflammation were noted in either study (Koenekoop, 2008).

In the Philadelphia study, subjects self-reported improved vision after two weeks. Statistically significant measurements such as increased visual fields, less time to complete obstacle courses, improved nystagmus frequency, and enhanced retinal sensitivity also showed that all three subjects' vision improved (Koenekoop, 2008; Maguire et al., 2008). In the London study, one participant had improved retinal sensitivity and had a reduced time to complete an obstacle course (Bainbridge et al., 2008; Koenekoop, 2008). The ability to read an ETDRS letter chart improved in one subject, but this was not statistically significant. However, two subjects had "no significant improvement in visual acuity" (Bainbridge et al., 2008; Koenekoop, 2008). ERG testing did not improve in any of the subjects of either study (Koenekoop, 2008).

A possible explanation for the lack of ERG improvement is that perhaps these subjects had already lost enough photoreceptor function that could not be restored. It was hypothesized that younger individuals, especially those before age 20, may show ERG improvements with treatment (Koenekoop, 2008). It was also possible that higher viral loads may have been more effective. The outcomes may have been different due to differing genotypes of the subjects, the promoters used with the AAV, or the presence of surfactant. Even though the studies had differing results, both showed that gene therapy could be used to treat LCA in a safe, effective manner. Additional trials over the years have expanded on the findings of these first two trials. Different AAV vectors and protocols were utilized with varying results. Certain trials showed initial vision improvement in subjects that then deteriorated back to baseline over time (Chao et

al., 2019). Other trials showed the efficacy of AVV treatments in children with no deterioration (Chao et al., 2019).

Luxturna is the brand name for voretigene neparvovec. Luxturna is an AAV vector (AAV2-hRPE65v2) that contains a human sequence of cDNA of a functioning *RPE65* gene that is injected into the subretinal space to treat individuals with bi-allelic pathogenic variants in *RPE65*. The drug is injected into each eye on separate days. Luxturna is a gene transfer therapy because a functional copy of the *RPE65* gene is transferred into a subject's affected tissues. The functional gene product acts to compensate for the loss-of-function manner of *RPE65* variants (Chao et al., 2019). Tissues treated with the AAV vector can produce functional proteins to ultimately help retain or improve vision. To qualify for treatment with Luxturna, individuals must be 1 to 65 years old with confirmed bi-allelic pathogenic variants in the *RPE65* gene. Luxturna is not recommended for those under 1 year old because retinal cells are still proliferating at high rates and the gene product may be lost ("Luxturna Timeline," 2017). Extensive ophthalmic evaluation must be performed, including an assessment of visual acuity and visual field, fundus measurements, and full-field electroretinogram (ERG) to measure any activity of the rods and cones (Chao et al., 2019). Optical coherence tomography (OCT), which is a measurement of the retina structure, is especially important since photoreceptors must retain some viability in order for gene transfer therapy to work effectively (Chao et al., 2019).

The Phase I trial for Luxturna lasted for two years and results were published in 2009. At the end of the trial, all twelve subjects had sustained visual improvement in areas of pupillometry, ERG results, and reduced nystagmus (Maguire et al., 2009). Another way to measure the efficacy of the treatment was measured using multi-luminance mobility testing (MLMT), which was a subject's ability to navigate around obstacles on a specific path with various light levels (Miraldi

Utz, Coussa, Antaki, & Traboulsi, 2018). Subjects were divided into three cohorts with different dosing levels, and improved vision was noted in all three cohorts (Maguire et al., 2009). Visual field expansion was greater in younger individuals, which was possibly because they had more viable photoreceptors than older subjects (Maguire et al., 2009). Adverse events included transient elevated intraocular pressure, cataracts, and retinal tears (Miraldi Utz et al., 2018). A report of a Phase II trial by Weleber et. al notes similar findings. The adverse events that occurred included subconjunctival hemorrhage and ocular hyperemia and were associated with the surgery itself, not a reaction to the AAV itself (Weleber et al., 2016). Nine of twelve subjects had improvement in at least one of the measured visual functions, and in general younger subjects had greater improvements (Weleber et al., 2016).

The Phase III trial utilized the MLMT measurement of navigating around obstacles in a path. Other assessments included eye charts, visual field assessments, foveal sensitivity threshold (FST), and pupillary light reflex (Russell et al., 2017). At the beginning of the trial, participants were divided into treatment and control groups. For the treatment group, Luxturna was injected into both eyes and results were compared to the untreated control group (Russell et al., 2017). Treated subjects showed improvement in MLMT and FST, which suggests improved light perception due to functional RPE65 proteins (Russell et al., 2017). This study also did not note any safety concerns related to the viral vector, and the procedure-related events were mostly transient or treatable (Russell et al., 2017). The results of light sensitivity, increased visual fields, and improved navigational ability, combined with the safety results, led to the FDA approval of Luxturna in 2017 (Miraldi Utz et al., 2018).

Although Luxturna has been FDA approved for over 3 years, there are still some considerations. Treating children is particularly concerning, since the FDA has approved treatment

for those over 1 years of age, but the youngest person included in trials was 4 years old (Miraldi Utz et al., 2018). Although it has been suggested that children may have the most to gain from this type of treatment, children under five may be more at risk for post-operative complications (Miraldi Utz et al., 2018). Another future consideration is treating seemingly autosomal dominant inheritance of *RPE65* pathogenic mutations. These cases have been reported but are currently not eligible for treatment since it is unsure if treatment would be effective (Miraldi Utz et al., 2018). Although the trial results have shown visual stability for three years or more, it is unknown how long a Luxturna treatment will be effective or if additional injections will be needed (Miraldi Utz et al., 2018).

## **2.4 SMA and Zolgensma**

Spinal muscular atrophy (SMA) is an autosomal recessive disease that affects the skeletal muscles. The alpha motor neurons in the anterior horn of the spinal cord degrade and are eventually lost, which leads to a muscle degeneration. SMA has a worldwide incidence of between 1/6000 to 1/10,000 live births and is a common cause of infant mortality (Serra-Juhe & Tizzano, 2019). Common symptoms of SMA are scoliosis, breathing and swallowing problems, muscle atrophy and areflexia, hand tremors, and tongue contractions. Individuals with SMA may require breathing assistance, a feeding tube or a mobility device like a wheelchair. Management is supportive and can include spinal surgery to treat or prevent scoliosis, back braces, and physical or occupational therapy. The manifestations and severity of symptoms depend on the type of SMA a patient has. There are five types of SMA. SMA type 0 is a rare presentation of SMA which presents with

reduced fetal movements and severe muscle weakness at birth (Al Dakhoul, 2017). Life expectancy of SMA type 0 is very short, with a range of days to weeks (Al Dakhoul, 2017). SMA type I accounts for about 60% of documented cases (Verhaart et al., 2017) and is the most severe type seen in living patients. Patients with SMA type I start showing symptoms at a few months old with hypotonia and muscle weakness that results in infants being unable to sit unsupported. If untreated, SMA type I will progress to death or require ventilation by about age 2 (Sugarman et al., 2012). SMA type II accounts for about 27% of documented cases (Sugarman et al., 2012) and has variable severity, with some patients being able to sit and others requiring mechanical support. Some patients have mild respiratory symptoms while others have severe respiratory issues (Sugarman et al., 2012). Patients with SMA type III may not be diagnosed until age 3 and often have trouble walking over time, but may or may not require wheelchair use. Patients with SMA type IV have mild muscle weakness and a slow disease progression.

All types of SMA are caused by bi-allelic mutations in the *SMN1* gene. About 95% of SMA cases are due to homozygous disruption of the *SMN1* gene, either due to a deletion of exon 7 or a conversion of *SMN1* to *SMN2* (Sugarman et al., 2012). *SMN2* is a pseudogene of *SMA1* and there is an inverse relationship between *SMN2* copy number and severity of phenotype. Although the correlation is not specific enough to predict the severity or onset of symptoms, in general, individuals with fewer copies of *SMN2* have more severe presentations and those with milder symptoms have more than 2 copies of *SMN2*.

Carrier frequencies for SMA vary based on ethnicity, and in the United States range from 1 in 47 for Caucasian individuals to 1 in 72 for African Americans (Sugarman et al., 2012). Since the carrier frequency was relatively high and there was accurate carrier screening available, in 2008 the American College of Medical Genetics (ACMG) created guidelines recommending that

SMA carrier screening be available to all pregnant couples (Sugarman et al., 2012). Other factors that lead to this recommendation included the severity of disease, availability of genetic counseling, and prenatal diagnosis (Sugarman et al., 2012). Although carrier screening was deemed to be sensitive and specific, there are challenges to assessing carrier status. Some individuals carry 2 copies of the *SMN1* gene on the same allele, which means that the second allele has 0 copies which can be passed on to their children. These individuals are called “silent carriers”. Carrier testing for “silent carriers” will show a false positive because they do have two copies of the *SMN1* gene, however, they can pass the deletion on to their children. The current carrier screening is completed via PCR or MLPA, which detects *SMN1* copy number. It cannot distinguish between non-carriers with two *SMN1* copies on opposite alleles and silent carriers.

Zolgensma (onasemnogene abeparvovec) is the gene transfer therapy that uses self-complementary adeno-associated viral serotype 9 (scAAV9) and was approved by the FDA in May 2019. It is a one-time intravenous infusion that was developed to treat SMA and halt disease progression by providing a functional copy of the *SMN1* gene to subjects. More than six hundred individuals have been treated with Zolgensma ("Novartis Provides Update on AVXS-101 Intrathecal Clinical Development Program," 2020). This treatment crosses the blood-brain barrier and is able to target neurons in all regions of the spinal cord (Mendell et al., 2017). Zolgensma was shown to allow a rapid and continuous expression of the functional SMN protein in multiple cell types, not only in the central nervous system but in organs like the heart and skeletal muscles (Mendell et al., 2017).

The first clinical trial for Zolgensma was run from 2014 to 2017. This was a study of fifteen subjects that was divided into two cohorts with different rates of dosing. Three of the participants received a “low dose” of  $6.7 \times 10^{13}$  vg per kilogram of body weight, while twelve of the participants

received a “high dose” of  $2.0 \times 10^{14}$  vg per kilogram of body weight (Mendell et al., 2017). When the data was collected in August of 2017, all fifteen subjects were alive, event free, and had better motor function than their untreated historical cohort which had a survival rate of 8% (Mendell et al., 2017). Motor function outcomes were measured using CHOP INTEND scores, which is a scale from 0 to 64 with higher scores reflecting better motor function. In particular, researchers assessed how long subjects could sit unassisted, if subjects could roll over, and other milestones such as speaking or walking (Mendell et al., 2017). All fifteen participants showed an increase in their CHOP INTEND scores, and eleven of the twelve subjects who received the higher dose were able to sit unassisted (Mendell et al., 2017). Nine of the subjects with the higher dosage could roll over and two walked without assistance (Mendell et al., 2017). None of the subjects with either dosage level required permanent mechanical ventilation (Mendell et al., 2017). In the two years that data was collected, there was no report of a decline in treatment efficacy (Mendell et al., 2017). This trial showed that there is a benefit of treating SMA with Zolgensma to slow or halt disease progression.

There were some adverse events in both dosage groups. The first subject who was treated had high levels of serum aminotransferase (Mendell et al., 2017). This was treated prednisolone while there were other liver-function abnormalities noted in their labwork, the subject did not have other clinical symptoms (Mendell et al., 2017). The protocol was amended after this occurred to treat subjects with oral prednisolone for the first thirty days after injection (Mendell et al., 2017). Three other subjects had elevated aminotransferase levels in their serum that was mitigated with prednisolone (Mendell et al., 2017). Fourteen of the fifteen participants had respiratory illness, which is likely related to the disease itself since it is a common cause of death in untreated infants



with SMA (Mendell et al., 2017). Aminotransferase levels and liver function is evaluated for all individuals being treated with Zolgensma, as this has been the most common adverse reaction.

There is another treatment that is currently available for SMA. Nusinersen (brand name Spinraza®) is an antisense oligonucleotide drug that causes alternate splicing to allow functional SMN protein to be made. It was approved by the FDA in December of 2016 and has shown to improve motor function in older individuals with SMA as well as allow children to reach developmental milestones (Dabbous et al., 2019; Serra-Juhe & Tizzano, 2019). Nusinersen requires multiple injections throughout the lifetime and does not cross the blood-brain barrier. Clinical trials have shown that both treatments improved patient survival rate, motor function, motor milestones, and decreased the need for assisted ventilation (Dabbous et al., 2019). No head-to-head trial was completed to compare Nusinersen and Zolgensma (Dabbous et al., 2019). Dabbous et al. performed a between-trial comparison to compare results between the two treatments and concluded that Zolgensma had a more favorable outcome for survival, motor function, and motor milestones (Dabbous et al., 2019). They also identified the advantage of a single intrathecal injection for Zolgensma as opposed to Nusinersen, which required multiple injections over a lifetime (Dabbous et al., 2019). However, a limitation of this comparison is that adverse effects were not analyzed by this group.

## **2.5 Roles of Genetic Counselors in the Context of Gene Therapy**

As gene therapies continue to be developed and become more clinically utilized, questions arise as to which health care providers should be involved in the treatment process and patient education. Clearly, genetic counselors could be involved in this process, especially if

molecular testing is needed to confirm a diagnosis or to confirm if gene therapy is appropriate. Counselors can discuss the benefits of genotyping patients with inherited retinal dystrophies (IRDs). Patient education regarding SMA, carrier status, and newborn screening are well-established responsibilities for genetic counselors. Genetic counselors are also well suited to provide patient education during the gene therapy treatment process. Typically medical doctors or specialists are tasked with talking about treatment details, patient surveillance, and overall management with patients and the responsibilities of genetic counselors as it relates to specific gene therapies is not clear.

In 1997, when gene therapy for cancer patients was starting to be considered, Dale Halsey Lea wrote an article regarding the potential for oncology nurses to be involved in treating patients who might receive gene therapy, and proposed that nurses would be best suited to talk to patients in depth about gene therapy treatments. The paper concluded, “Oncology nurses will need to become knowledgeable about the methods and applications of gene therapy for cancer to participate in clinical trials and to develop relevant nursing management plans” (Lea, 1997). Lea identified numerous responsibilities for oncology nurses who are involved in the care of individuals undergoing gene therapy. Included in those responsibilities are items such as providing anticipatory guidance, providing information to patients in an understandable way, gathering family history, assessing psychosocial factors that may impact care, assisting in a decision-making process and obtaining informed consent, and providing psychosocial support. Assisting patients and their families as they made choices regarding genetic testing or treatments, cooperating with other members of a treatment team, and ensuring continuity of care were listed as duties of oncology nurses (Lea, 1997). They also listed items such as providing information to family members, education of the public, advocating for equitable use of gene

therapies, and participating in conversations regarding the ethical and safety factors surrounding developing treatments. These are the same responsibilities that genetic counselors have to their patients. Therefore, it seems that genetic counselors are appropriate providers of this information and would be valuable assets on a healthcare team for individuals considering gene therapy. It is also important to realize that this paper was written before genetic counselors were commonly involved in oncology cases, so oncology nurses were taking on many roles that are now performed by cancer genetic counselors. Although this was written from a perspective of providing care to cancer patients, these ideas can be applied to genetic counselors working in any kind of practice- cancer, prenatal, pediatrics, or other specialties.

Veach, Bartels and LeRoy surveyed providers, including genetic counselors, regarding the challenges professionals face when serving patients with genetic disorders. The main challenge identified, from all professional backgrounds, was regarding informed consent, which Veach et al define as, “situations in which the professional questioned the extent to which she or he had communicated the most relevant information for a given patient, the extent to which the patient was able to comprehend this information, and the voluntariness of the patient’s decision” (Veach, Bartels, & LeRoy, 2001). Participants identified time constraints, professional biases, and lack of patient understanding as the main obstacles to obtaining true informed consent. These are obstacles that genetic counselors have been trained to overcome. As part of training, genetic counselors are encouraged to break down large ideas into understandable pieces of information to allow patient comprehension. Time management and non-directiveness are also key pieces of training in the genetic counseling field. Therefore, it seems that genetic counselors are well suited to take on the challenge of obtaining informed consent for patients considering gene therapies.

However, genetic counselors questioned their roles in a variety of settings and the extent of their involvement in traditional healthcare settings. Genetic counselors answered that at times, they were uncertain about their professional role, and felt conflicted regarding their relationships with colleagues or with patients (Veach et al., 2001). One categorical answer described genetic counselors as “being caught in the middle—the professional is torn between the patient’s wishes and the wishes of other professionals” (Veach et al., 2001). Providers were also unsure on “how far to go in providing services to patients” (Veach et al., 2001). If genetic counselors are having professional identity issues in the context of well established clinics and typical counseling settings, it can be assumed that these will be challenges moving forward into new domains such as gene therapy as well.

These studies demonstrate that genetic counselors believe that genetics professionals need to be involved in patient care in order to ensure that patients received proper care. The suggested levels of involvement were: ensuring that patients and families had to correct information and that the correct screening or testing options were presented. Respondents suggested that a team or multidisciplinary approach was the best suited for proper patient care (Bensend et al., 2014). Survey respondents made suggestions to prevent negative outcomes. One theme that was identified was changing institutional processes. Suggestions included making access to genetic counselors easier, and integrating genetic counselors into the healthcare team on a daily or on an as-needed basis (Bensend et al., 2014). This suggests a team approach would benefit all parties: the physician, the genetic counselor, and most importantly, the patient. Although this study looked at genetic counselors’ opinions of “genetic services” and not gene therapies specifically, it is feasible to think that genetic counselors may have similar opinions on who should be involved in discussions regarding Luxturna and Zolgensma.

The need for genetic professionals to collaborate with other healthcare providers remains a concern for genetic counselors. Bensend et al. surveyed genetic counselors in 2010 and 2011 to explore the negative patient outcomes that occurred when genetic counseling was provided by professionals without genetic training. The Bensend project drew from multiple studies that previously indicated health care providers without genetic specific training were not equipped to provide genetic services (Bensend, Veach, & Niendorf, 2014). In particular, studies over the years have shown that primary care providers do not have the correct training to assess risk of genetic conditions from a pedigree, were unaware of risks to other family members and may fail in their duty to warn, or to make the correct referrals to genetic specialists (Bensend et al., 2014). Surveyed participants identified multiple possible negative outcomes to receiving inadequate genetic counseling care. These negative outcomes impacted the patients, the health care system, and the providers themselves. Patients who did not receive proper counseling and information had negative psychosocial impacts including confusion, increased anxiety, and frustration (Bensend et al., 2014). This correlated to patients reporting negative attitudes and mistrust towards their providers. Providers at times ordered the wrong genetic test or screen, gave incorrect medical management advice, or misused healthcare resources.

## **2.6 Current Knowledge and Actual Experiences**

In 2015, Ganne et al. led a study that showed that eye care professionals do not have the correct training to fully counsel on gene therapy treatments for eye disease and could benefit from working with a genetic counselor. This study assessed how well primary eye care providers, undergraduate optometry students, and the public understood genetic testing and gene

therapy. While 82% of the respondents felt that genetics was important, only 35% of them felt that they understood genetics, and none of them had a “high level of understanding of genetics and inherited eye diseases” (Ganne, Garrioch, & Votruba, 2015). The vast majority of respondents, 70%, answered that genetic counseling would be helpful for patients (Ganne et al., 2015). These rates were similar across all three participant groups: the eye care professionals, the students, and the public. This is especially important since Ganne et al. also concluded that the general public looks favorably on genetic testing and gene therapy, provided they are counseled with the correct information (Ganne et al., 2015).

A survey of health care providers was conducted by Frontline Medical Communications in collaboration with the National Organization for Rare Disorders (NORD). At the time of publication, which was March 2020, there were four FDA-approved gene therapies: Kymriah to treat leukemia, Luxterna to treat retinal dystrophy, Yescarta to treat lymphoma, and Zolgensma to treat Spinal Muscular Atrophy. While most respondents were physicians (MDs or DOs), nurse practitioners and other providers answered as well. Of the 1,472 participants, 87% were physicians and 13% were family practice providers. When asked what would cause barriers for patients being treated with gene therapies, cost was the most common answer. The “need for staff training” and “potential burden for patients both immediate consequences and longer term follow up requirements” were also identified as major barriers (Rare Neurological Disease Special Report, March 2020).

The results of the survey showed that 63% of participants did not know about the available therapies. The NORD report states, “Despite an impressive rate of contact with patients who have rare genetic diseases, responses indicated that knowledge about gene therapy is limited” (Rare Neurological Disease Special Report, March 2020). 54% of participants had at

least one patient with a genetic disorder, and 45% reported having made a referral for genetic or biochemical testing (Rare Neurological Disease Special Report, March 2020). Participants responded that they were not comfortable talking about gene therapies with patients. Instead, most providers preferred to refer patients to experts. Only 20% of respondents reported discussing gene therapies or clinical trials with their patients (Rare Neurological Disease Special Report, March 2020). Of this set of respondents, 45% were hematology/oncology specialists and 43% were neurology specialists (Rare Neurological Disease Special Report, March 2020). This suggested that specialists who are in areas of practice with current FDA approved gene therapies are far more likely to understand and be comfortable discussing gene therapy treatment than general practitioners.

Awareness of therapies showed similar trends. The NORD report states, “The respondents most aware of these options were specialists in hematology/oncology (87%), neurology/child neurology (71%), rheumatology (56%), and pediatrics (42%), while dermatology showed least awareness (17%)” (Neurological Disease Special Report, March 2020). Fifty-four percent of participants identified “limited knowledge among health care professionals” as a barrier to gene therapy for patients and 32% of participants reported that they had not sought out any type of education on gene therapies or clinical trials (Rare Neurological Disease Special Report, March 2020). When asked what could cause genetic mutations, no provider selected all of the correct answers (Rare Neurological Disease Special Report, March 2020). Similarly, no provider correctly chose all options when answering what the possible effects of pathogenic variants could be (Rare Neurological Disease Special Report, March 2020). Only 24% of participants reported being able to explain the differences between somatic and germline mutations, and 52% of participants were unsure or unaware that somatic mutations are

not able to be inherited (Rare Neurological Disease Special Report, March 2020). The NORD survey determined that providers would benefit from additional education regarding genetic disorders and potential treatments.

None of the respondents in the NORD survey were genetic counselors or medical geneticists. To date, there has not been extensive research regarding how familiar genetic counselors are with these emerging treatments. A study was conducted in 2019 to assess the comfort levels of prenatal genetic counselors regarding Spinraza, a type of treatment used for treating Spinal Muscular Atrophy. Although Spinraza and Zolgensma work in different manners, the information gained from this study was a starting point to assess what information genetic counselors already know about treatments for SMA and how that information is used in patient sessions. 182 prenatal genetic counselors in the United States were surveyed to assess “knowledge of nusinersen [Spinraza], access to information, and attitudes towards discussing this therapy in practice” (Zettler, 2019). The results of the study showed that while 73.6% of participants knew “a little bit” or “quite a bit” about Spinraza, while 5.5% had never even heard of it (Zettler, 2019).

This survey also tried to assess under what circumstances genetic counselors discuss Spinraza. Only 15.4% of genetic counselors reported that they were “extremely” likely to discuss Spinraza (Zettler, 2019). Counselors were most likely to bring up the drug in the setting of a positive prenatal diagnosis, followed by if both parents were confirmed SMA carriers. This suggested that treatments are more likely to be discussed when there was a strong indication. However, even when there was a prenatal diagnosis of SMA, only 82.2% of respondents reported that they would discuss Spinraza (Zettler, 2019). The Zettler study suggested that when genetic counselors were familiar with Spinraza or had access to SMA specialists, they were more



likely to discuss Spinraza with patients. Survey results also showed that many genetic counselors were unsure of where to refer patients, where to find reliable information, and what details to provide to patients.

To evaluate how this knowledge could be used in a genetic counseling session, a prenatal clinical scenario was presented in a stepwise fashion. Participants rated how likely they were to discuss specific topics during certain parts of the scenario. Only 2.2% of respondents were “extremely unlikely” to discuss Spinraza in the scenario of a positive prenatal SMA diagnosis (Zettler, 2019). Of that set of respondents, 75% reported that they had never heard of Spinraza before (Zettler, 2019). This suggests that counselors who have no knowledge of treatments will not be able to discuss said treatments with patients. To summarize the findings, the prenatal genetic counselors who were likely to discuss Spinraza in the earlier parts of the genetic counseling session had a better background knowledge of the treatment and were more likely to have access to SMA specialists or treatments in their area of practice. This survey showed that even genetic counselors, who have a concrete knowledge of genetic mechanisms and inheritance, are not familiar with this new avenue of therapy.

## **2.7 The Need for Training and Policies**

One of Zettler’s conclusions was “that GCs who are unsure of options available to their patients are also unable to find reliable information on their own, indicating an unmet need for increased education” (Zettler, 2019). Zettler suggested that educational materials, improved communications, and practice guidelines are needed to help keep genetic counselors up to date with therapies like Spinraza. Both Spinraza and Zolgensma have been approved for less than five

years and no professional organization has developed practice guidelines or educational materials regarding these treatments. As such, there is no one place for genetic counselors to gather information or seek guidance outside of information from the manufacturers or clinical trial publications. It is imperative that genetic counselors be able to research and find suitable resources regarding gene therapies, because treatments are being developed so rapidly that they cannot be expected to know all of the most up-to-date information available.

Respondents in the Veach study identified challenges in attaining and maintaining proficiency, especially difficulties keeping up with new genetic technologies and information (Veach et al., 2001). Genetic counselors answered that it was important to maintain proficiency in ever-changing genetic test availability and protocols, to know current patient resources, and to be cognizant of standards of care (Veach et al., 2001). As more gene therapies are developed, trialed, and put into clinical practice, it remains imperative that individuals introducing treatment options remain current in their knowledge base. This domain can be applied to future challenges providers will face as gene therapies become more common. Determining the correct test for a patient can be difficult- for example, providers need to decide whether to order *RPE65* single gene analysis since there is currently a treatment, or a larger panel to have more information if other treatments are developed in the future. Another facet of this second point is that patients can be very motivated to seek treatments themselves, and counselors “expressed difficulty responding to patients who bring up new tests or treatments that they found from the internet or other media, especially when the participants had never heard of these tests and had no way to evaluate their quality or appropriateness” (Veach et al., 2001). In the future, genetic counselors will need to take steps to be prepared to answer these patient concerns or to investigate information patients are bringing in, and perhaps correct some misconceptions. Genetic

counselors will need specific training and resources to be able to stay up to date on emerging clinical trials and where to refer patients to the correct resources.

Currently, NSGC and ACMG have not made educational resources or policy statements regarding gene transfer therapies. ACMG's board of directors issued a statement in 2017 regarding gene editing, referencing the potential for CRISPR/Cas9 methods. Their position was that the technical limitations and ethical conundrums should be thoroughly explored before this technology could be used in a clinical setting (Board Of Directors, 2017). However, it does not mention roles of genetic counselors in this process. The statement does not reference gene transfer therapies at all, and was made before the approval of Luxturna and Zolgensma. Since there is no policy statement or guidelines regarding gene transfer therapies, genetic counselors do not have guidelines on their responsibilities or roles in treating patients with gene transfer therapies. This means that the type of counseling and level of detail provided varies greatly among genetic counselors. A policy statement or universal training could provide some consistency among genetic counselors' practices.

### 3.0 Manuscript

#### 3.1 Background

There are currently two FDA approved gene transfer therapies: Zolgensma (onasemnogene abeparvovec-xioi) to treat Spinal Muscular Atrophy and Luxturna (voretigene neparvovec-rzyl) to treat *RPE65* Associated Inherited Retinal Dystrophy. Gene transfer therapy works by inserting a working copy of the gene of interest into a viral vector made from a virus which is then injected into a patient's affected tissue so that functional proteins can be made. Viral vectors that have been trialed include adenoviruses, adeno-associated viruses, retroviruses, and herpes simplex. While it may seem natural for genetic counselors to be involved in the care of patients who may benefit from these treatments, there are no practice guidelines or educational tools regarding gene therapies designed for genetic counselors. Research shows that most healthcare providers are not knowledgeable regarding gene therapies, but the comfort level of genetic counselors has not been studied. It is unclear if the availability of these two treatments, as well as the development of gene transfer therapies for other conditions, has an impact on genetic counseling sessions or changes the way genetic counselors practice.

## **3.2 Methods**

### **3.2.1 Study Design**

A survey was developed by the research team to measure the knowledge and comfort level that genetic counselors have regarding gene transfer therapies, to assess if there were differences among certain demographic groups, and to investigate if the availability of gene transfer therapies impacted genetic counseling sessions. The survey was piloted by the research team and by three genetic counselors, and then sent through Qualtrics to collect anonymous responses. The survey was sent through the National Society of Genetic Counselors (NSGC) student research listserv. Two recruitment emails were sent through NSGC two weeks apart. Additional recruitment emails were sent to informal ophthalmology and hematology genetic counselor email groups. An email invitation was sent to a metabolic provider listserv, which included genetic counselors and other medical providers. This was the only opportunity for providers who were not genetic counselors to see the survey. Recruitment emails were also directly sent to a handful of genetic counselors of varying specialties. Each email included a description of the purpose of study, a link to the survey, and the author's contact information, which is included as Appendix B. Participant answers were collected by Qualtrics for five weeks from January to March of 2021. This was approved by the University of Pittsburgh Institutional Review Board (IRB) and was determined to be exempt research. The IRB exempt letter is included as Appendix A.

Inclusion criteria required respondents to be board-certified or board-eligible genetic counselors working in North America. The survey consisted of 22 questions and is included as Appendix C. Questions were multiple choice, open-ended, and Likert-scale. The first block of questions was regarding demographics. Participants were required to answer if they were board-

certified or board-eligible, and individuals who answered no were not able to answer any other questions. The demographics block also asked about years of experience and specialties practiced. The next block of questions was regarding experiences with gene therapies. Likert-scales and open-ended questions were used to assess the participants' familiarity, comfort level, and frequency of discussion regarding gene therapies. Participants were required to answer these questions for Zolgensma and Luxturna, and there was an optional opportunity to describe other therapies. Another block of questions was meant to assess genetic counselors' feelings, attitudes, and experiences regarding gene therapies, as well as the perceived impact of these treatments on counseling sessions. The last block of questions was centered on any education or training that genetic counselors have received, as well as any education or training opportunities they would appreciate in the future. All questions were optional unless noted above.

### **3.2.2 Statistical Analysis**

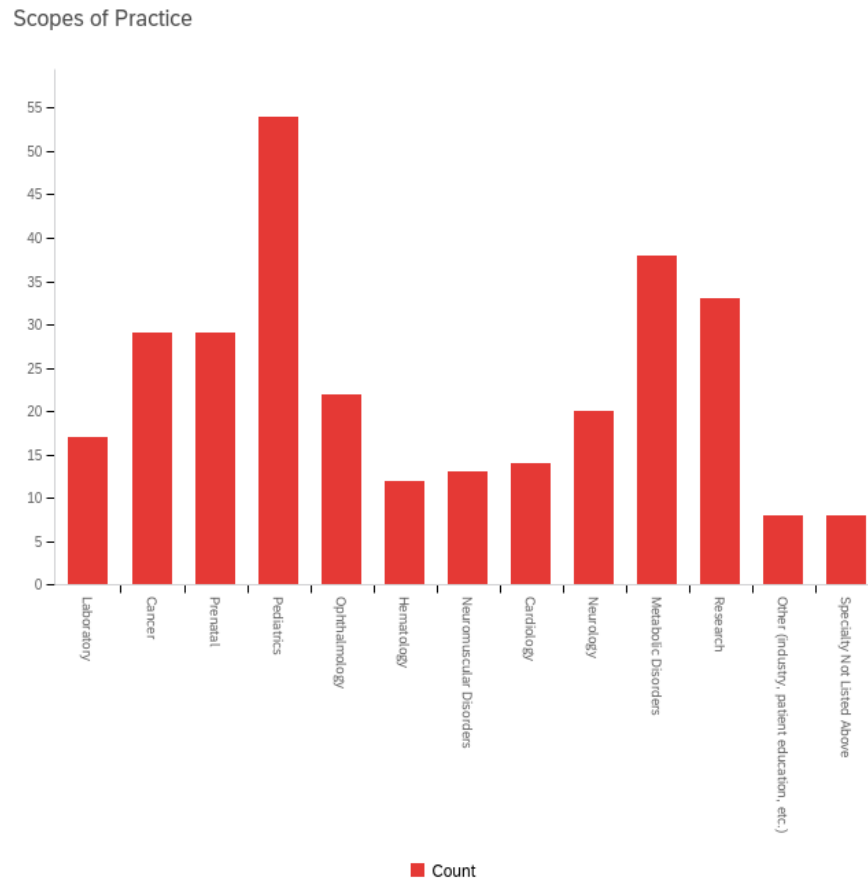
Statistical analysis included descriptive statistics, 2 sample Z tests, and chi squared analyses. The answers to open-ended questions were collected and sorted into themes. Analysis was completed using Stata SE 16, Qualtrics and Microsoft Excel.

### **3.3 Results**

#### **3.3.1 Demographics**

There were 113 responses to the survey. A total of 109 genetic counselors completed the survey; 4 respondents were excluded because they answered that they were not board-eligible or board-certified genetic counselors working in the United States or Canada. When asked about years of experience, 107 genetic counselors answered. Forty six respondents graduated between 1 and 5 years ago, while another 14 graduated less than a year ago. This means that 56% of those that answered this question (60 out of 107) graduated 5 years ago or less, and responses did skew to more recent graduates.

Participants were able to select as many scopes of practice as they had worked in during their career. The most common area of practice was pediatrics, with 54 respondents selecting that answer. The second most common area of practice was metabolic disorders, with 38 respondents selecting that answer. Twenty nine respondents each answered prenatal and cancer. Twenty two participants worked in ophthalmology, 12 participants worked in hematology, and 13 participants answered that they worked with neuromuscular disorders. This was reassuring that genetic counselors who work with neuromuscular conditions were not underrepresented, even though there was no recruitment email sent to them specifically. Sixteen individuals selected “other” or “specialty not listed above” and were able to describe their practice. These descriptions were: industry, health IT, consulting, report writing, neurofibromatosis, general adult, translational medicine, newborn screening, mitochondrial disease, public health, PGD, inpatient, and skeletal. Scopes of practice are further described in Figure 1 below.



**Figure 1: Scopes of Practice Bar Chart**

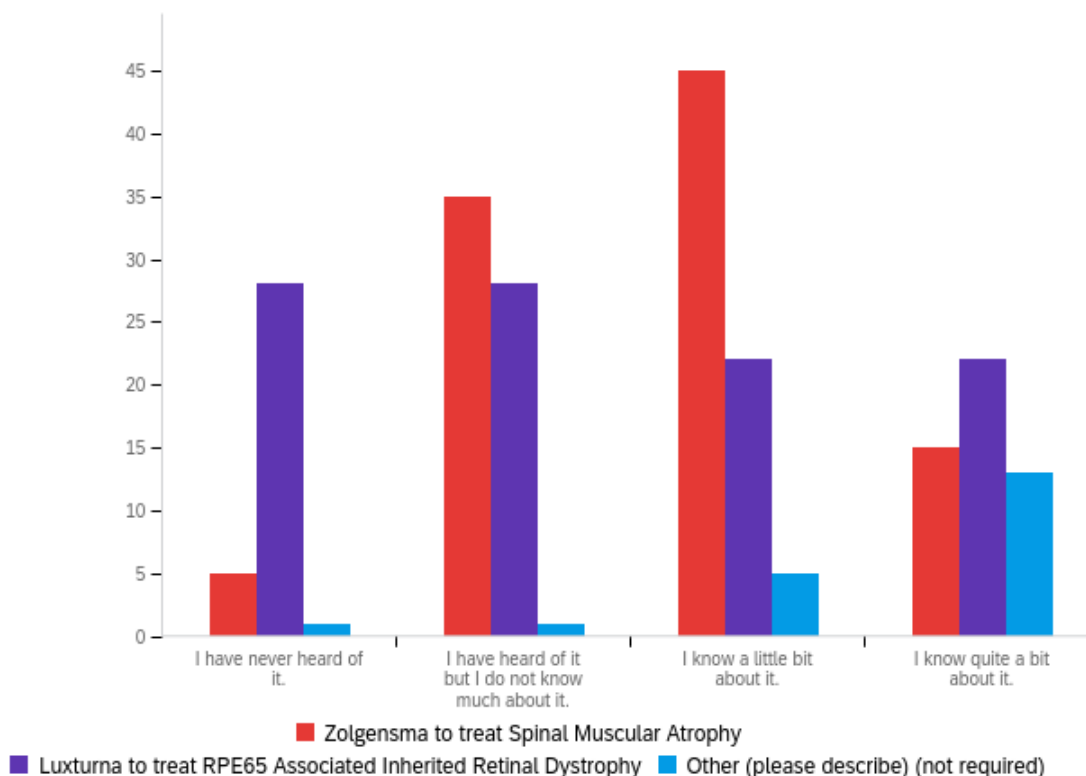
### 3.3.2 Knowledge and Comfort Level

When asked how familiar the participants were with gene therapies, respondents were required to answer for Zolgensma and Luxturna and had the option to select “other” and describe other therapies. Five participants had “never heard of” Zolgensma, and 35 participants selected “I have heard of it but do not know much about it”. The most common answer (45%) was “I know a little bit about” Zolgensma, with 45 participants selecting this choice. Only 15 participants answered that they knew “quite a bit” about this treatment. For Luxturna, 28 participants each



answered that they had “never heard of it” or did “not know much about it.” 22 participants each answered that they knew “a little bit” or “quite a bit” about Luxturna.

How familiar are you with...



**Figure 2: Familiarity with Therapies**

These answers were further divided by specialty and are listed in Table 2. Chi squared analysis showed that, for both therapies, there is evidence to suggest the true proportions of familiarity levels are not homogeneous across specialty (p-value < 0.0001 for both Zolgensma and Luxturna). For example, 16 of the 21 ophthalmology counselors answered that they knew “quite a bit about” Luxturna. When looking at how counselors working in pediatrics answered for Zolgensma, 15 answered that they did “not know much about it” and 26 answered that they knew “a little bit about it.” There were 30 participants who selected that they worked in research. These counselors answered that they knew “quite a bit about” Luxturna 12 times and Zolgensma 8 times.

Therefore, someone's specialty does affect how likely they are to be familiar with Luxturna and Zolgensma.

**Table 1: Familiarity with Zolgensma and Luxturna Breakdown by Specialty**

		<i>...never heard of it.</i>		<i>I have heard of it...</i>		<i>I know a little bit...</i>		<i>I know quite a bit...</i>	
		Zolgensma	Luxturna	Zolgensma	Luxturna	Zolgensma	Luxturna	Zolgensma	Luxturna
Laboratory	14	0	4	5	2	5	5	4	3
Cancer	27	3	10	15	11	7	4	2	2
Prenatal	27	1	10	10	11	11	4	5	2
Pediatrics	50	1	15	15	16	26	10	8	9
Ophthalmology	21	1	1	8	3	10	1	2	16
Hematology	11	0	4	7	4	3	2	1	1
Neuromuscular	13	0	3	2	4	6	3	5	3
Cardiology	14	1	4	6	7	5	2	2	1
Neurology	19	0	1	4	6	6	6	9	6
Metabolic	35	1	11	12	13	19	11	3	0
Research	30	2	6	10	6	10	6	8	12
Not Listed	8	0	2	3	2	4	3	1	1
Other	7	1	1	1	2	3	2	2	2
<b>Specialty</b>	<b>Total</b>								

**Table 2: Familiarity with "Other" Therapies Breakdown by Specialty**

		<i>I have never heard of it.</i>	<i>I have heard of it...</i>	<i>I know a little bit...</i>	<i>I know quite a bit...</i>
Laboratory	1	0	0	0	1
Cancer	3	0	0	0	3
Prenatal	5	1	0	1	3
Pediatrics	11	1	0	3	7
Ophthalmology	2	0	0	1	1
Hematology	3	0	0	0	3
Neuromuscular	2	0	0	0	2
Cardiology	2	0	0	1	1
Neurology	1	0	0	0	1
Metabolic	9	0	0	3	6
Research	9	0	0	2	7
Not Listed	2	0	0	1	1
Other	3	0	0	0	3
<b>Specialty</b>	<b>Total</b>				

Twenty participants elected to respond to familiarity of “other” gene therapies. Of those 20 respondents, 1 person each selected they had “never heard” of another therapy or that they did “not know much” about it. Five participants (25% of those who selected “other”) said they knew “a little bit” about the therapy they described, and 13 participants (65%) said they knew “quite a bit” about it. When these answers were divided by specialty and evaluated with chi square analysis, the results were not significant ( $p\text{-value} = 0.167$ ). Text entries for this answer could be divided into two categories: those that have current trials or ongoing research, and those that are not technically gene therapies. Participants described research for gene therapies for conditions such as Duchenne muscular dystrophy, hemophilia, sickle cell disease, thalassemia, lysosomal storage disorders, metabolic conditions, severe combined immunodeficiency, familial dysautonomia, and Leber hereditary optic neuropathy. Answers to the “other” option also described treatments for genetic disorders that were not truly gene therapies, including mitochondrial replacement, Evrysdi (risdiplam) and Spinraza (nusinersen) for SMA, exon skipping for Duchenne muscular dystrophy, and “biochemical patients”.

When these answers were divided by years of experience, there was evidence to suggest the levels of familiarity were not homogeneous across years of experience (see Figure 6 in Appendix D). Sixty percent of those who graduated less than a year ago and 75% of those who graduated 25 or more years ago answered that they knew “a little bit about” Zolgensma ( $p\text{-value} < 0.0001$ ). In contrast, 23% of those who graduated less than a year ago and 50% of those who graduated 25 or more years ago answered that they had “never heard of” Luxturna ( $p\text{-value} < 0.0001$ ). Therefore, someone’s years of experience does affect their familiarity with gene therapies.

Participants were also required to answer how comfortable they would be discussing gene therapies with a patient. The most common response for both treatments was “slightly comfortable”, with 51% of participants selecting this option for Zolgensma and 45% for Luxturna. With regards to the 20 respondents who chose to respond regarding their comfort level for “other” therapies, 11 said they were “very comfortable” and only 1 said they were “not comfortable”.

**Table 3: Comfort Level with Zolgensma and Luxturna Breakdown by Specialty**

		<i>Not comfortable...</i>		<i>Slightly comfortable...</i>		<i>Moderately comfortable...</i>		<i>Very comfortable...</i>	
		<b>Zolgensma</b>	<b>Luxturna</b>	<b>Zolgensma</b>	<b>Luxturna</b>	<b>Zolgensma</b>	<b>Luxturna</b>	<b>Zolgensma</b>	<b>Luxturna</b>
Laboratory	14	1	2	4	6	7	4	2	2
Cancer	27	3	6	16	15	8	4	0	2
Prenatal	27	2	7	14	15	10	3	1	2
Pediatrics	50	3	11	24	23	18	11	5	5
Ophthalmology	21	3	0	13	3	4	4	1	14
Hematology	11	0	3	7	3	3	4	1	1
Neuromuscular	13	0	2	6	5	3	4	4	2
Cardiology	14	0	3	10	7	4	4	0	0
Neurology	19	0	3	6	5	10	7	3	4
Metabolic	35	4	13	18	15	13	7	0	0
Research	30	4	3	9	9	14	7	3	11
Not Listed	8	1	3	4	3	3	2	0	0
Other	7	0	0	3	2	3	4	1	1
<b>Specialty</b>	<b>Total</b>								

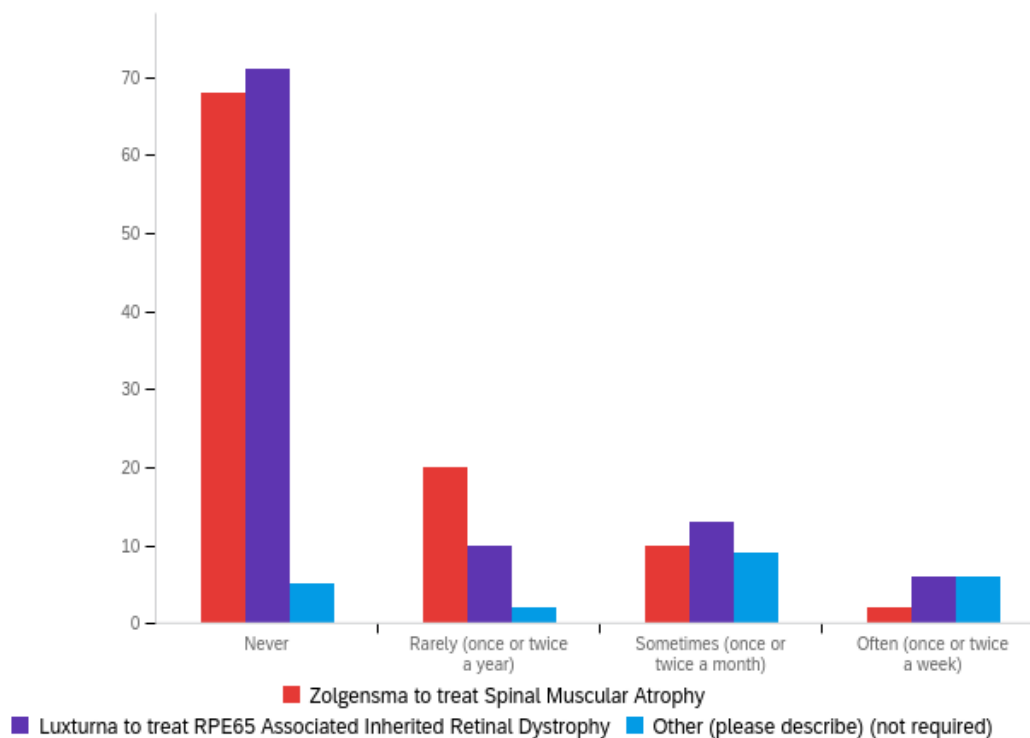
Chi squared analysis showed that someone’s specialty does affect how likely they are to be comfortable discussing Luxturna and Zolgensma with patients (p-value < 0.0001 for both treatments). For example, 67% of ophthalmology counselors, 7% of cancer counselors, and 7% prenatal counselors answered that they were “very comfortable” with Luxturna. When asked about Zolgensma, 37% of prenatal counselors, 50% of laboratory counselors, and 53% of neurology counselors answered that they were “moderately comfortable.” There was no statistical significance to the differences between specialties when they answered how familiar they were with “other” therapies.

There is also evidence to suggest the true proportions of comfort levels are not homogeneous across years of experience. Twenty one percent of those with 6-10 years of experience answered that they were “not comfortable” with Zolgensma and Luxturna and 25% of those with 25 or greater years of experience answered they were “not comfortable” with Zolgensma and Luxturna. This contrasts with counselors with 1-5 years of experience, since only 5% answered that they were “not comfortable” with Zolgensma and 12% answered that they were “not comfortable” with Luxturna. This heterogeneity in comfort levels was seen with all three answer options (chi-squared analysis: p-value for Zolgensma < 0.0001, p-value for Luxturna < 0.0001, p-value for “other” therapies = 0.008). Therefore, someone’s years of experience does affect how likely they are to be comfortable talking about Luxturna, Zolgensma, or “other” therapies with patients.

To assess the actual experiences that genetic counselors have had, participants ranked how often they discussed the gene therapies with a patient, from never to often. Eighty eight percent of participants answered that they “never” or “rarely” discussed Zolgensma with a patient. Ten percent of participants said they “sometimes” discussed Zolgensma and only 2% said they discussed this “often.” Eighty one percent of participants answered that they “never” or “rarely” discussed Luxturna with a patient. Thirteen percent of participants said they “sometimes” discuss Luxturna and only 6% said they discuss this “often.” While the rates of answers were similar for the first two therapies, the trend was different for the 22 participants who answered “other” therapies. Twenty three percent of these responses were “never” and 9% were “rarely” (5 and 2 participants respectively). Forty one percent answered that they “sometimes” discussed other therapies (9 participants) and 27% answered that they “often” discussed other therapies (6 participants). There was evidence to suggest that genetic counselors from different specialties

discuss Zolgensma and Luxturna at different frequencies (chi squared analysis: p-value for Zolgensma < 0.0001, p-value for Luxturna = 0.001). Therefore, someone's specialty does affect how frequently they discuss Luxturna and Zolgensma with patients.

How often do you directly discuss the follow gene therapies with a patient?



**Figure 3: How Often do you Discuss Gene Therapies**

Participants were asked to summarize their familiarity with gene therapies and their experiences discussing them with patients, which were then sorted into common themes. Some participants answered that they never discussed gene therapies. One participant said, *"I have not seen patients clinically for 10 years...I would have to do a major literature review etc. as part of the learning process for a new role but am confident that my GC training prepared me for this learning."* Other participants described scenarios in which they either discussed general information with patients or discussed gene therapy in detail. One counselor described how they encounter both of these scenarios in their practice as, *"I work in an inherited retinal dystrophies*

*clinic, so we discuss Luxturna with all patient [sic] who come back with RPE65 variants, maybe 1 or 2 a year. However, we also discuss it in a more vague sense much more frequently as an example of how gene therapy works, and one of the potential benefits of proceeding with genetic testing for their IRD.” Other participants agreed that they only discussed therapies when a patient tested positive, for example, “It would be me who talks about gene therapy, but only for patients who are found to have a child with SMA. I have not had anyone have a child with SMA. The only time I have discussed it is with couples who are both carriers of SMA in a prenatal setting.” Other counselors described their experience as being knowledgeable about trials, research, or how to make the proper referrals. Answers that fall into these themes include, “Patients in ophthalmology often express an interest to participate in research or want to know about new therapies so I often talk about gene therapies and clinical trials at least briefly with patients. I attend webinars and read journal articles related to gene therapies in ophthalmology so I am able to answer patient questions about research and new treatments” and “I have made one SMA dx in pediatrics and discussed Zolgensma briefly and made the appropriate referral to neurology for treatment/further discussion.”*

### **3.3.3 Feelings, Attitudes, Experiences and Impact**

The participants were asked how important they felt it was for genetic counselors to know about available gene therapies. Seventy nine percent of participants answered “extremely important” or “very important.” Participants were asked to choose which providers should feel comfortable discussing gene therapies with patients and were allowed to select multiple answers. Ninety seven participants responded to this question. Ninety five respondents selected “geneticist” (98%), 90 respondents selected “genetic counselor” (95%), and 88 respondents selected a

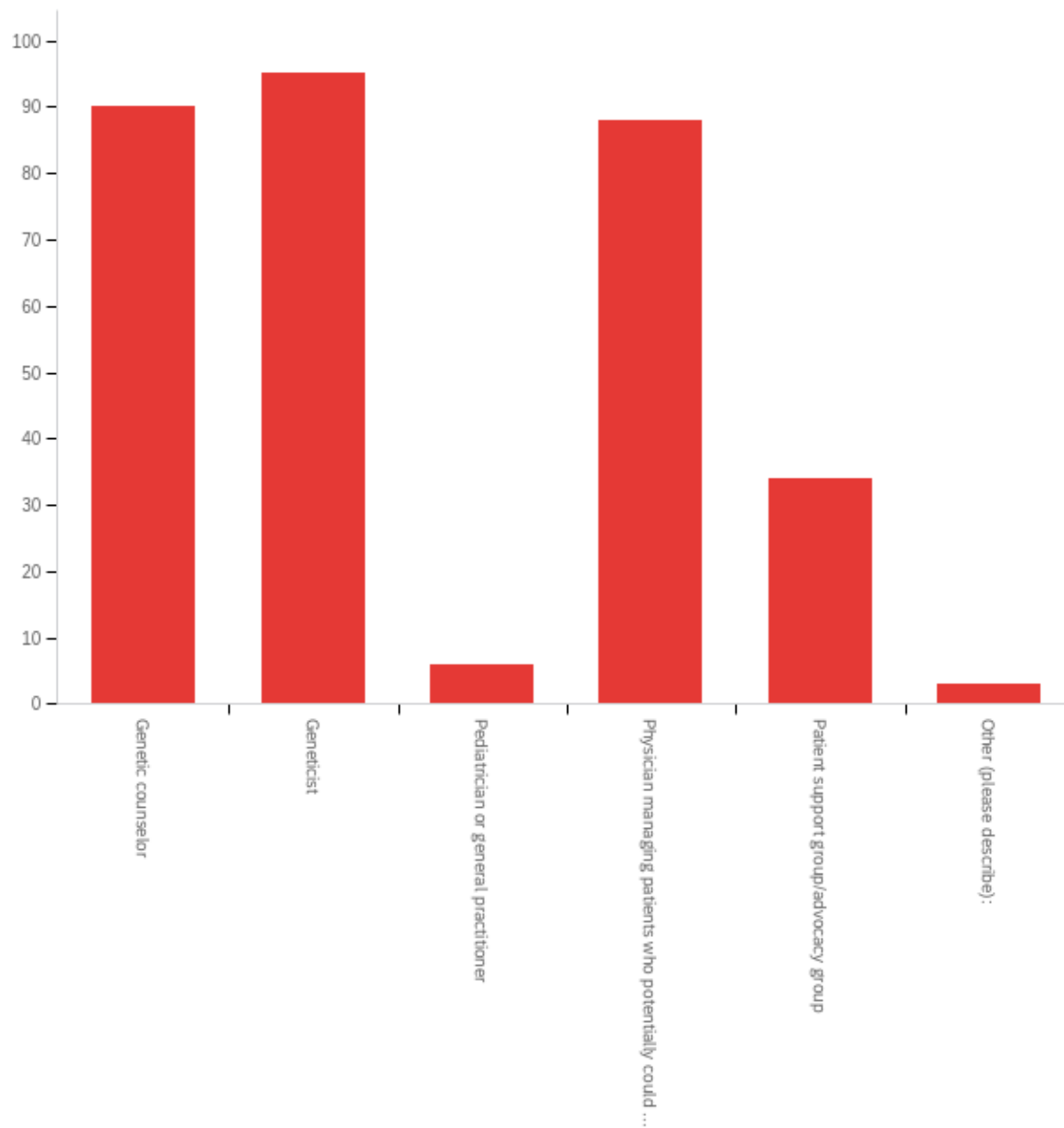
“physician that may work with patients, such as a neurologist or ophthalmologist” (93%). All of the 90 respondents who chose “genetic counselor” also selected other providers. Forty three of the 90 participants who chose “genetic counselor” answered that it was “very important” for genetic counselors to know about available therapies. These responses suggest that genetic counselors should be involved in patients who may be treated with gene therapies as part of a team approach with multiple providers.

**Table 4: Importance of Genetic Counselors Knowing About Gene Therapies**

<b>Answer</b>	<b>Percentage of Responses</b>	<b>Count</b>
Extremely important	32.99%	32
Very important	46.39%	45
Moderately important	17.53%	17
Slightly important	2.06%	2



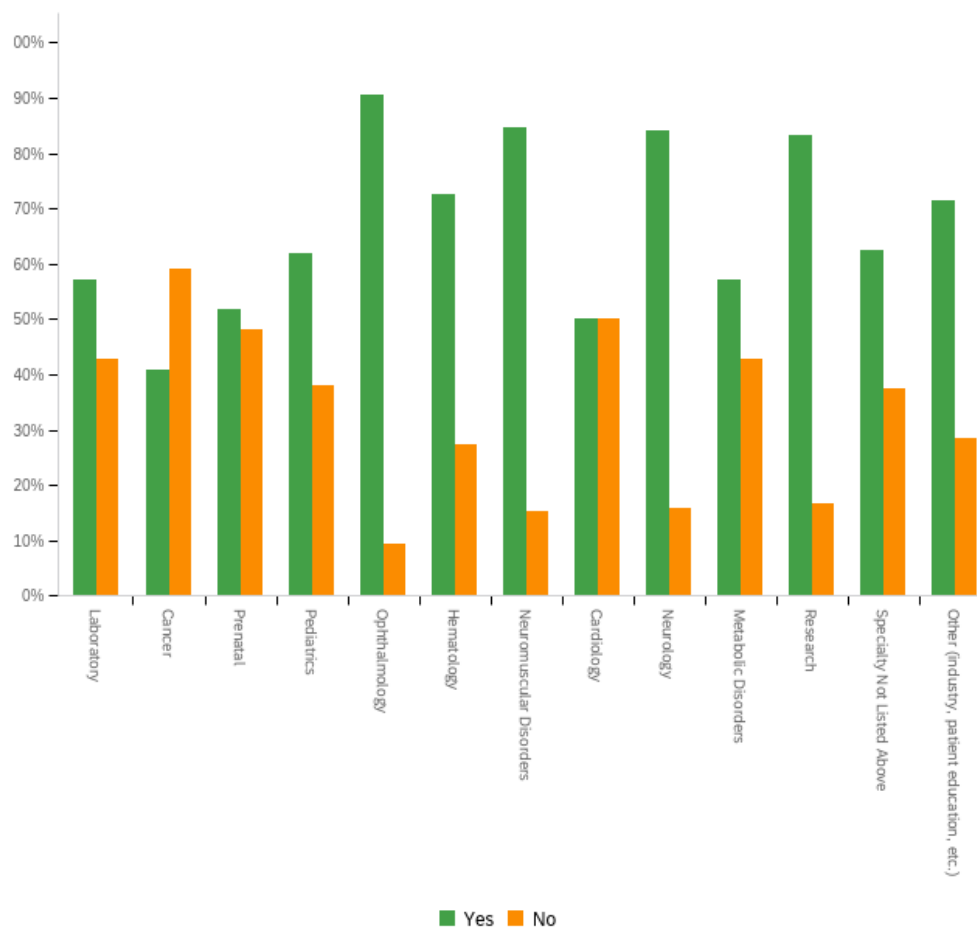
Which providers should feel comfortable discussing gene therapies with patients?



**Figure 4: Which Providers Should Feel Comfortable Discussing Gene Therapies**

When asked if counselors felt that the availability of gene therapies had directly impacted their work or practice, 59% responded “yes” and 41% responded “no” (58 and 40 responses, respectively). Answers varied based on specialty. For example, 91% of ophthalmology counselors (a 2 sample z test comparing this specialty to the collective answers resulted in a p-value = 0.0057), 85% of neuromuscular counselors (2 sample z test p-value = 0.1325) and 84% of neurology genetic counselors (2 sample z test p-value = 0.0716) said “yes.” The only specialty group that was more likely to answer “no” was cancer genetic counselors, where only 41% responded “yes” (2 sample z test p-value = 0.0716).

Has the availability of gene therapies directly impacted your work? Breakdown by Specialty:



**Figure 5: Impact of Gene Therapies Breakdown by Specialty**

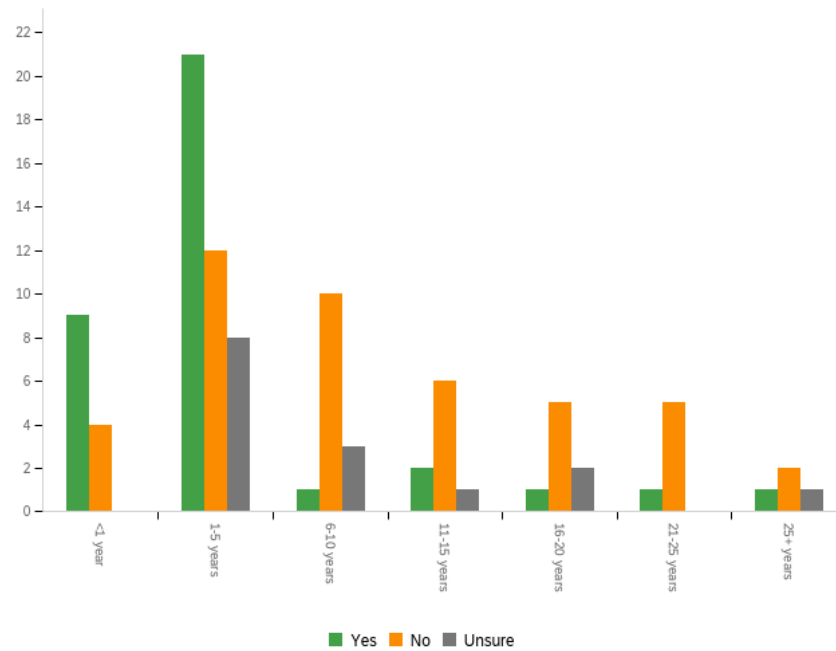
Respondents also described how gene therapies impacted their work or practice in short answers. The themes that emerged were that patients themselves bring therapies up, hope for potential treatment, changes to the interest level and manner for genetic testing, and pop culture or media. One counselor stated, *“The vast majority of my patients have heard about gene therapy research in hematology at their local advocacy group, national meeting, in the news, and in peer social media groups. They always ask me for updates about the status thus it behooves me to be up to date and have an answer.”* Multiple responses mentioned that patients were more hopeful and optimistic due to the availability of treatment, even if there was not a treatment for their specific condition. One participant described how they are more optimistic as a provider now, saying that before Luxturna, *““untreatable” was the word for all inherited retinal degenerations. This state of affairs and inability to offer some limited hope did take a toll [on me, psychologically] day after day, patient after patient.”* One response that addresses the themes of hope and increased interest in testing is, *“The availability of Luxturna has not only drastically impacted the lives of a few of my patients, but has also provided hope to the entire patient community, and changed the enthusiasm for the IRD patient community to undergo genetic testing.”* In regards to how Zolgensma has changed testing, counselors described that testing for SMA is more frequent and more rapid since there is a desire to detect the condition earlier and before symptoms progress. Carrier testing is now available to all pregnant patients and SMA has been added to some newborn screens, both of which respondents have attributed in part to treatments being available. Counselors also described how Luxturna has allowed testing for inherited retinal dystrophies (IRDs) to be expanded and allows for variants in genes besides *RPE65* to be detected.

Participants were asked to describe the roles that genetic counselors may play in the future, especially as gene therapies become more readily available. Almost every answer described the same roles that genetic counselors have typically taken on. Responses included, *“providing psychosocial support and counseling to them in their journey of considering/pursuing gene therapy”* and *“One role is balancing expectations for the availability of gene therapies. I sometimes have patients seeking genetic testing for the sole reason of hoping for a gene therapy. Often the physician (e.g. ophthalmologist) can oversell the possibility prior to the patient undergoing genetic testing and their mutation even being known (may not be a candidate).”* Responsibilities such as obtaining informed consent, providing anticipatory guidance, educating patients and their families, and coordinating appropriate referrals were included.

### **3.3.4 Education and Training**

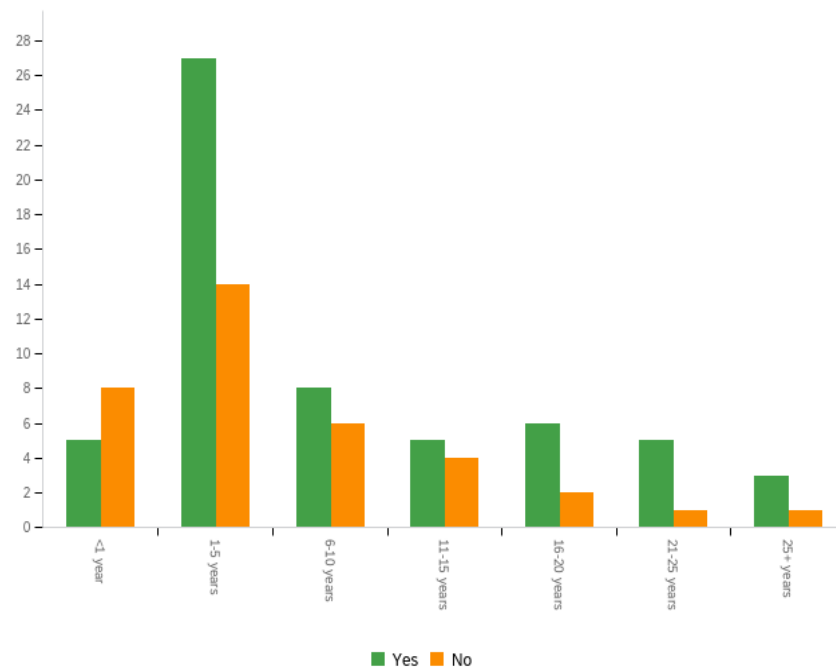
When asked if the participants received training about gene therapies in their genetic counseling program, 36 participants said “yes,” 44 participants said “no,” and 15 said “unsure.” When separated by years of experience, participants with five years of experience or less were more likely to answer “yes” than “no” (chi square analysis:  $p\text{-value} < 0.0001$ ). Participants also answered if they had received any training or continuing education hours regarding gene therapies. Except for those who graduated less than a year ago, all experience ranges were more likely to answer that “yes” they have attended trainings (chi square analysis:  $p\text{-value} < 0.0001$ ). Participants were then prompted to select as many hosts and methods of trainings they had previously attended. The most common answers for who hosted the trainings was “NSGC” with 39 responses and “drug manufacturers” with 35 responses. 58 participants said they attended a “seminar or lecture” and 30 selected “workplace discussion.”

Did your genetic counseling program provide training? Breakdown by Years of Experience



**Figure 6: Training Provided by Genetic Counseling Program Breakdown by Years of Experience**

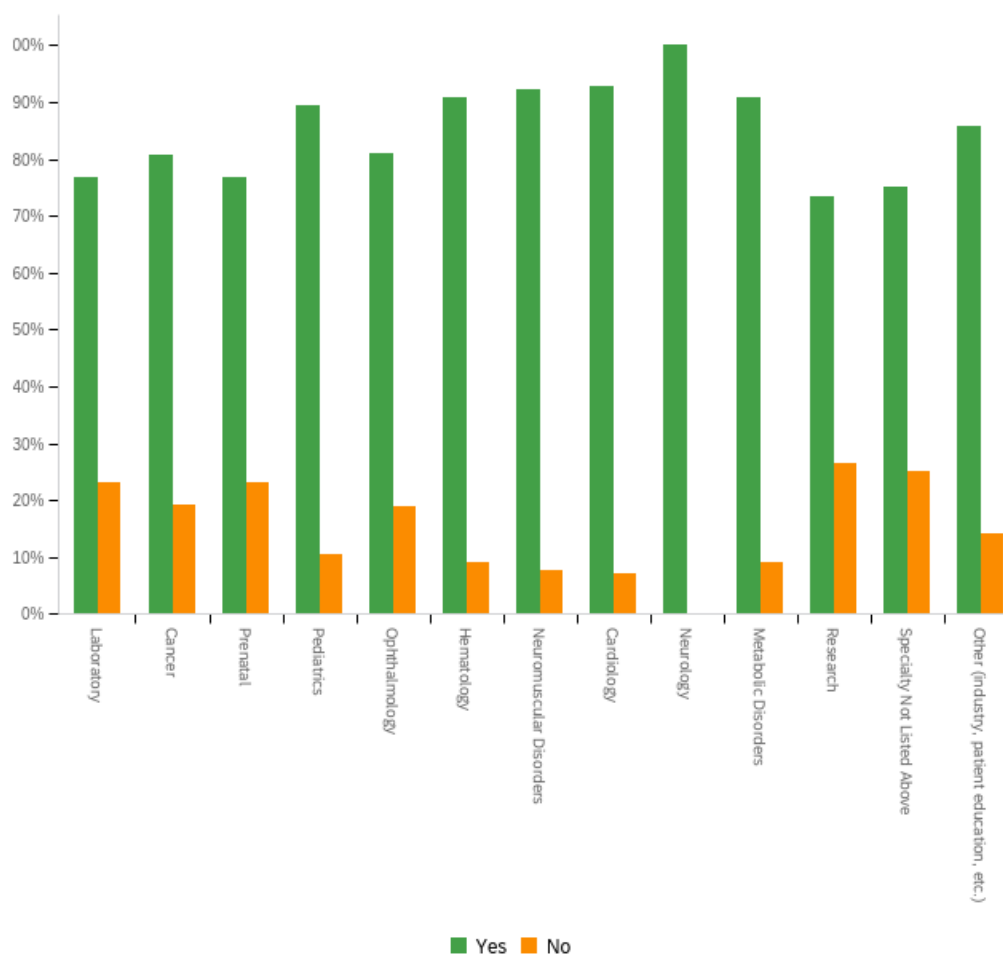
Have you attended any trainings or continuing education hours regarding gene therapies?  
Breakdown by Years of Experience



**Figure 7: Attendance of Trainings Breakdown by Years of Experience Bar Chart**

When asked if they would be interested in additional education, 79 respondents answered “yes” and 16 said “no”. Participants were more likely to say “yes” than “no,” regardless of years of experience (see Figure 9 in Appendix D). 61 participants answered that “NSGC” would be an appropriate provider for future trainings, 60 answered “scientific journal articles,” and 55 answered “other professional organizational training.” 50 total participants answered either training through the workplace or discussion with colleagues. “Popular media” received 0 responses. The most common answer for preferred training method was “seminar or lecture,” with 76 responses, followed by 53 respondents selecting “online training.”

Would you be interested in additional training/education? Breakdown by Specialty:



**Figure 8: Interest in Additional Training Breakdown by Specialty**

### 3.4 Discussion

Results from this survey suggest that genetic counselors believe they can be important members of the healthcare team caring for patients considering gene therapies. Previous studies have determined that genetic counselors are frequently assessing their ever-changing professional relationships to other providers (Bensend et al., 2014) and their roles on a healthcare team (Veatch et al., 2001). Respondents in the Bensend study suggested that a multidisciplinary approach would be most beneficial for patient care and could avoid negative outcomes (Bensend et al., 2014). Although most respondents did not frequently discuss gene therapies with patients, the majority of participants in this study answered that they felt it was important for genetic counselors to be knowledgeable about available gene therapies and that genetic counselors should feel comfortable discussing gene therapies with patients. Counselors in almost every specialty felt that the availability of gene therapies directly impacted their practice.

Recent graduates reported that their genetic counseling program provided training on gene therapy more frequently than those with more years of experience. This is possibly due to the fact that FDA approvals for Zolgensma and Luxturna were in 2019 and 2017, respectively ("Novartis Provides Update on AVXS-101 Intrathecal Clinical Development Program," 2020; (Miraldi Utz et al., 2018). However, even for recent graduates, high proportions of participants responded that they did not have training during their graduate program or were unsure. Genetic counseling programs follow curriculum standards set by ACGC, which at this time does not mention gene therapies, but does include case management (Accreditation Counsel for Genetic Counseling, 2019). This shows the possibility for training on gene therapies to be integrated into the curriculum of genetic counseling programs.

Except for genetic counselors with less than a year of experience, the majority of participants had attended training outside of graduate school for gene therapies. It is possible that this is a reflection that those who graduated recently are still working on certification, cannot get educational credits before they are certified, or have had less time to attend training. It may also be due to the increased likelihood that recent graduates had training during their graduate program. Professional training through organizations such as NSGC or through the workplace, scientific journals, and seminars or online training were all identified as appropriate opportunities for genetic counselors.

Counselors from every specialty answered that they would appreciate more education, even those who were very familiar with the therapies such as respondents from ophthalmology or those who answered “other” therapies. Responses from those in specialties who reported they were not comfortable and did not discuss therapies with patients (such as cancer) were also interested in more training. Participants also described multiple instances that they sought out information or training in order to be prepared for genetic counseling sessions in their short answer responses. The Zettler study had similar responses from prenatal genetic counselors regarding Spinraza, with around 5% of respondents having never heard of the treatment and only around 15% of counselors answering that they were extremely likely to discuss the treatment after a diagnosis of SMA (Zettler 2019). All of this suggests that genetic counselors would appreciate additional educational opportunities.

Of the 20 participants who described the “other” therapies they were familiar with, 7 of the responses were not technically gene therapies. They were all treatments for genetic disorders, but it is important to consider why these answers were included. It is possible that genetic counselors do not know the distinctions between gene therapies and other treatments. Certainly, the general



population may not know these technical differences and could consider treatments like DMD exon skipping “gene therapy.” It is also possible that counselors do know the differences but are used to reflecting patient language and describing these treatments in the same conversations as gene therapies. The survey specifically did not define “gene therapy” or “gene transfer therapy” in the introduction and language in order to determine if these sorts of answers would be included.

Previous studies have shown that healthcare providers who do not specialize in genetics do not have adequate knowledge regarding genetic disease, inheritance, or treatment (Ganne et al., 2015; Rare Neurological Disease Special Report, March 2020). This suggests that genetic counselors could fill that knowledge gap and have a beneficial role on a healthcare team for patients eligible for gene therapies. When asked which providers should feel comfortable discussing gene therapies with patients, 90% of participants answered that counselors, geneticists, and physicians should be involved. No one selected only one provider. This data demonstrates that genetic counselors desire to be on the healthcare team having these conversations about gene therapies with patients.

### **3.5 Limitations**

There are some limitations to this study. The 2020 NSGC conference hosted sessions for Zolgensma and Luxturna specifically, and NSGC special interest groups have also held trainings on gene therapies. It is possible that NSGC members have more educational opportunities than genetic counselors who are not members. Since recruitment emails were sent through the NSGC listserv, it is possible that there is some bias in the results.

Another limitation is the small sample size of 109 responses. The United States Government Accountability Office reported that there were 5,169 certified genetic counselors in North America as of 2019 (United States Government Accountability Office, 2020), which means that just above 2% of eligible counselors responded to this survey. It is also possible that certain scopes of practice that frequently work with patients who are eligible for these treatments are overrepresented.

### **3.6 Future Implications**

This project introduced some questions that were not able to be fully explored. For example, future studies could be done to explore if genetic counselors do know the different classifications of various treatments that address the underlying genetic mutation. It was not possible to separate these answers based on whether genetic counselors had easy access to treatment centers where gene therapies are administered. Additional studies could be performed to clarify the current responsibilities of genetic counselors that work in treatment centers or are involved in clinical trials. A similar survey could be distributed to the general public or to patients to see how they would answer these questions. It would be helpful to learn what information patients already know and what role patients would want genetic counselors to perform. This information could be used to develop additional guidelines or training for genetic counselors, either as educational seminars or to be implemented in genetic counseling program curricula.

### **3.7 Conclusions**

The conclusions that can be drawn from these results support the original hypotheses and aims. Genetic counselors in certain specialties (such as cancer) are less likely to know about gene therapies and to discuss them with patients. Genetic counselors in other specialties (such as ophthalmology or research) are more likely to know about gene therapies and are more likely to discuss them with patients. Respondents believe that counselors should be knowledgeable about gene therapies and described how counselors should be able to provide counseling for these patients, including informed consent, anticipatory guidance, education and referrals. Gene transfer therapies have already impacted genetic counseling sessions for some respondents. Counselors do seek out training regarding gene therapy and would appreciate additional educational opportunities.

#### **4.0 Research Significance to Genetic Counseling and Public Health**

Assurance is a core function of public health. Two essential public health services that fall under assurance are to improve assurance through evaluation and research and to build a skilled workforce. This study was the first step in evaluating the education level and skills of genetic counselors regarding gene therapies. Fifty nine participants had attended some kind of training and 79 participants were interested in additional educational opportunities. When asked about future trainings, the most common hosts selected were NSGC or other professional organizations (61 and 55 responses, respectively), scientific journal articles and drug manufacturers (60 and 45 responses, respectively). Seminars, lectures, and online trainings were the most common responses for method of training, which totaled 129 answers. Only 36 respondents answered that their genetic counseling program trained them on gene therapy. There may be opportunities for genetic counseling programs to provide education on gene therapies. It may also be possible to integrate treatments into the core competencies of genetic counseling training. Additional studies can build on these results to improve assurance.

Another service of public health is to diagnose health hazards under the core function of assessment. Many of the respondents of this survey described their roles as genetic counselors in identifying a patient's genetic cause for inherited retinal dystrophies, identifying SMA carriers, or confirming an SMA diagnosis. It is clear that genetic counselors are already a key part of assessing patients that may be eligible for gene therapies. There is potential for genetic counselors to expand these responsibilities and improve assessment by correctly identifying patients and families who may benefit from gene transfer therapies. Genetic counselors already strive for equitable access to genetic services, to educate the general public, and to empower patients and their families, all of

which can be done in the context of gene transfer therapies. This study illustrated that counseling on gene therapy treatments is a natural extension of the counseling already being provided.

## Appendix A IRB Exemption Letter

### *IRB Exemption Letter*



### EXEMPT DETERMINATION

Date:	October 26, 2020
IRB:	STUDY20100152
PI:	Chelsey Walsh
Title:	An Assessment of Genetic Counselors' Knowledge and Attitudes Regarding Gene Transfer Therapies
Funding:	None

The Institutional Review Board reviewed and determined the above referenced study meets the regulatory requirements for exempt research under 45 CFR 46.104.

#### Determination Documentation

Determination Date:	10/26/2020
Exempt Category:	(2)(i) Tests, surveys, interviews, or observation (non-identifiable)
Approved Documents:	<ul style="list-style-type: none"><li>• Survey Gene_Transfer_Therapies tracked changes.docx, Category: Data Collection;</li><li>• Exemption Worksheet Chelsey Walsh, Category: IRB Protocol;</li><li>• Recruitment Text CW, Category: Recruitment Materials;</li><li>• Walsh Summary of Intent, Category: Other;</li></ul>

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, [Teresa McKaveney](#).

Please take a moment to complete our [Satisfaction Survey](#) as we appreciate your feedback.

## **Appendix B Recruitment Text**

*Recruitment Text that was included in all invitation emails*

Dear genetic counselor,

You are being invited to participate in a survey being conducted by Chelsey Walsh as part of a thesis requirement for the University of Pittsburgh Genetic Counseling Program.

This survey is meant to assess the current knowledge and attitudes that genetic counselors have regarding gene therapies. Questions are centered on the two currently FDA approved gene therapies Zolgensma and Luxturna. There will be opportunities to describe your experience with other gene therapies (such as those still in clinical trials) as well.

The questionnaire should take between 10-20 minutes to complete. There are no foreseeable risks associated with this project, nor are there any direct benefits to you. This is a confidential questionnaire. Your participation is voluntary and you do not have to complete or submit the survey.

Chelsey can be reached at cnw30@pitt.edu if you have any questions.

To participate in this research study, please click the link below to access the survey:

[https://pitt.co1.qualtrics.com/jfe/form/SV\\_bCVZWNGypNEqBaB](https://pitt.co1.qualtrics.com/jfe/form/SV_bCVZWNGypNEqBaB)

## Appendix C Survey

### *Gene Therapies Survey*

#### **Introduction Statement**

Q1 Thank you for your interest in this research study. This survey is meant to assess the current knowledge and attitudes that genetic counselors have regarding gene therapies. Questions are centered on the two currently FDA approved gene therapies Zolgensma (onasemnogene abeparvovec-xioi) and Luxturna (voretigene neparvovec-rzyl). There will be opportunities to describe your experience with other gene therapies (such as those still in clinical trials) as well.

The questionnaire should take between 10-20 minutes to complete. There are no foreseeable risks associated with this project, nor are there any direct benefits to you. This is a confidential questionnaire. Your participation is voluntary and you do not have to complete or submit the survey.

This study is being conducted by Chelsey Walsh as part of a thesis requirement for the University of Pittsburgh Genetic Counseling Program. Chelsey can be reached at cnw30@pitt.edu if you have any questions.

#### **Demographics**

Q2 Are you an ABGC or CAGC board-certified or board-eligible genetic counselor?

☐ Yes

☐ No

*Skip To: End of Survey If Q2 = No*



Q3 How many years of experience do you have as a practicing genetic counselor?

☐ < 1 year

☐ 1-5 years

☐ 6-10 years

☐ 11-15 years

☐ 16-20 years

☐ 21-25 years

☐ 25+ years

Q4 Please check all scopes of practice you have worked in throughout your entire career:

☐ Laboratory

☐ Cancer

☐ Prenatal

☐ Pediatrics

☐ Ophthalmology

☐ Hematology

- ☐ Neuromuscular Disorders
- ☐ Cardiology
- ☐ Neurology
- ☐ Metabolic Disorders
- ☐ Research
- ☐ Specialty Not Listed Above
- ☐ Other (industry, patient education, etc.)

### Statement

Q5 If you are genetic counselor that does not regularly see patients (i.e. laboratory or research), please substitute “patient” with “client” or “other healthcare provider” to answer the rest of the survey's questions.

### Experiences

Q6 How familiar are you with the following gene therapies?

	I have never heard of it.	I have heard of it but I do not know much about it.	I know a little bit about it.	I know quite a bit about it.

Zolgensma to treat Spinal Muscular Atrophy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Luxturna to treat RPE65 Associated Inherited Retinal Dystrophy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Other (please describe) (not required)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q7 How comfortable are you discussing the following gene therapies with a patient?

	Not comfortable: I could not answer questions or find more resources.	Slightly comfortable: I could not answer questions in the moment but I would know where look up information after the session.	Moderately comfortable: I could probably answer some questions or find more information for them.	Very comfortable: I could probably answer many questions and point them to appropriate resources.
Zolgensma to treat Spinal Muscular Atrophy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Luxturna to treat RPE65 Associated Inherited Retinal Dystrophy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Other (please describe) (not required)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q8 How often do you directly discuss the following gene therapies with a patient?

	Never	Rarely (once or twice a year)	Sometimes (once or twice a month)	Often (once or twice a week)
Zolgensma to treat Spinal Muscular Atrophy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Luxturna to treat RPE65 Associated Inherited Retinal Dystrophy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Other (please describe) (not required)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q9 Please summarize your familiarity with gene therapies and/or your experiences discussing them with patients (i.e. who initiates talking about gene therapy, in what context does it come up, what level of detail can you provide):

**Feelings, Attitudes, Experiences and Impact**

Q10 How important do you feel it is for genetic counselors to know about available gene therapies for genetic conditions?

- ☐ Extremely important
- ☐ Very important
- ☐ Moderately important
- ☐ Slightly important
- ☐ Not important

Q11 Which providers/individuals should feel comfortable discussing gene therapies with patients?

Check all that apply:

- ☐ Genetic counselor
- ☐ Geneticist
- ☐ Pediatrician or general practitioner
- ☐ Physician managing patients who potentially could be treated with gene therapy (ex: neurologist or ophthalmologist)
- ☐ Patient support group/advocacy group
- ☐ Other (please describe):

Q12 Do you feel that the availability of gene therapies has directly impacted your work/practice as a genetic counselor?

- ☐ Yes
- ☐ No

*Skip To: Q14 If Q12 = No*

Q13 Please describe how gene therapies have impacted your work/practice as a genetic counselor:

Q14 As gene therapies become more readily available, what role do you see genetic counselors playing?

**Education/Training**

Q15 Did your genetic counseling program provide any training regarding gene therapies?

☐ Yes

☐ No

☐ Unsure

Q16 Have you attended any trainings/continuing education hours regarding gene therapies?

☐ Yes

☐ No

*Skip To: Q20 If Q16 = No*

Q17 Who hosted the training(s)? Check all that apply:

- ☐ Drug manufacturers
- ☐ A patient advocacy group
- ☐ NSGC
- ☐ Other professional organizational training
- ☐ Training through your workplace
- ☐ Word of mouth/discussions with colleagues
- ☐ Popular media (TV, newspaper, magazines, etc.)
- ☐ Scientific journal articles
- ☐ FDA
- ☐ Other (please describe):

Q18 What was the method of training(s)? Check all that apply:

- ☐ Brochure/written literature
- ☐ Seminar/lecture
- ☐ Sales pitch



☐ Workplace discussion

☐ Online training

☐ Other (please describe):

Q19 Please briefly describe the training/educational experience:

Q20 Would you be interested in additional training/education regarding gene therapies?

☐ Yes

☐ No

*Skip To: End of Survey If Q20 = No*

Q21 Who is the most appropriate provider for trainings/education? Check all that apply:

- ☐ Drug manufacturers
- ☐ A patient advocacy group
- ☐ NSGC
- ☐ Other professional organizational training
- ☐ Training through your workplace
- ☐ Word of mouth/discussions with colleagues
- ☐ Popular media (TV, newspaper, magazines, etc.)
- ☐ Scientific journal articles
- ☐ FDA
- ☐ Other (please describe):

Q22 What method would you prefer for trainings/education? Check all that apply:

☐ Brochure/written literature

☐ Seminar/lecture

☐ Sales pitch

☐ Workplace discussion

☐ Online training

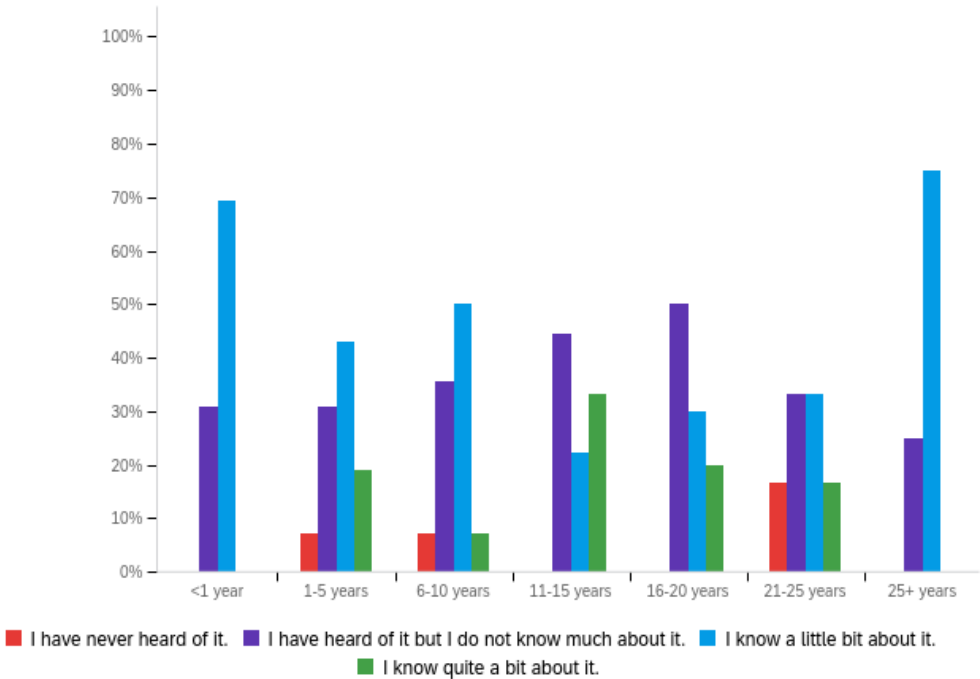
☐ Other (please describe):

## **Appendix D Supplementary Tables and Figures**

### *Supplementary Tables and Figures*

How familiar are you with the Following Therapies Breakdown by Experience

Zolgensma to treat Spinal Muscular Atrophy



Luxturna to treat RPE65 Associated Inherited Retinal Dystrophy

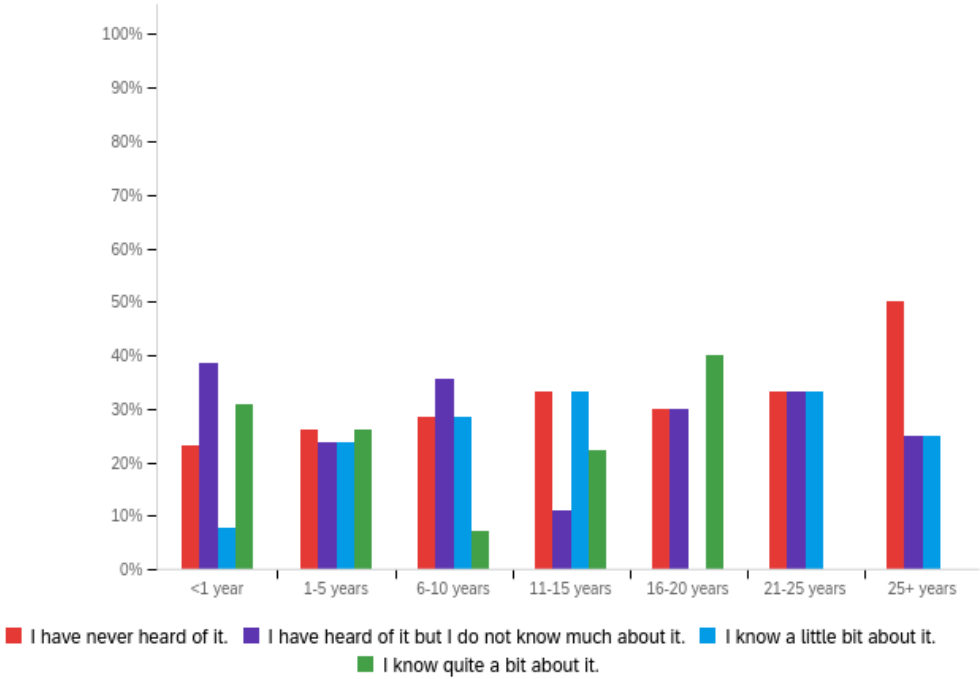
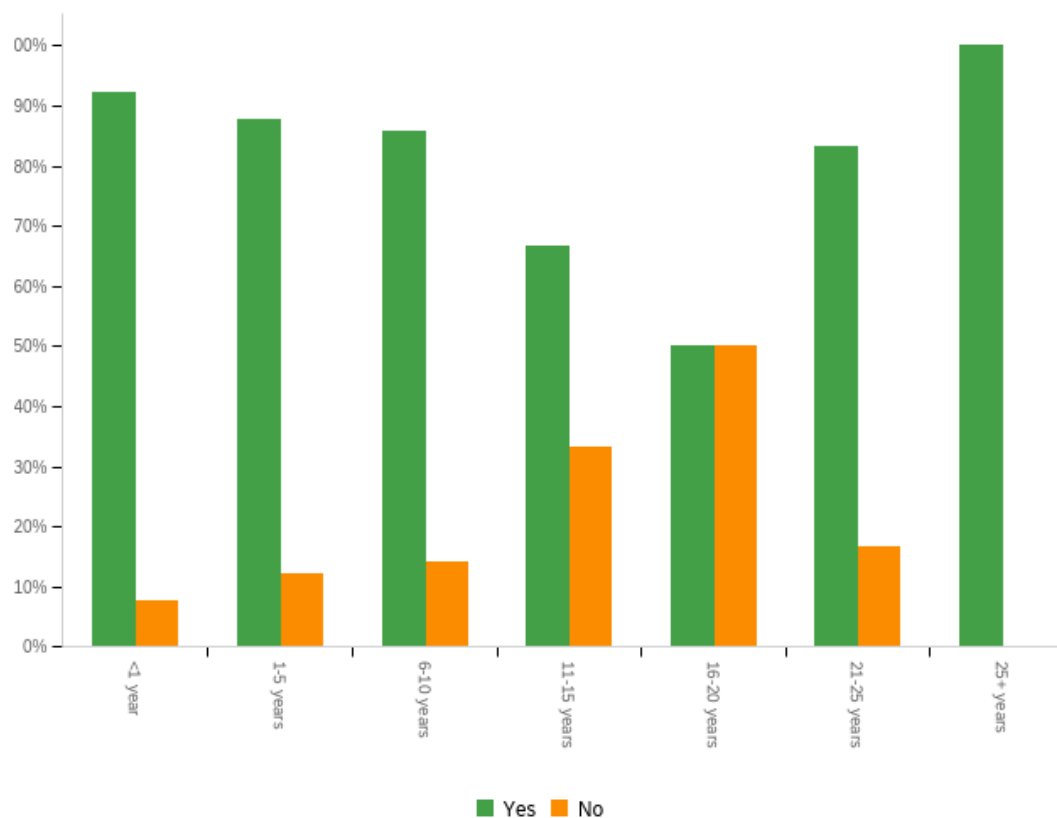


Figure 9: Familiarity with Zolgensma and Luxturna Breakdown by Experience

Would you be interested in additional training/education? Breakdown by Years of Experience:



**Figure 10: Interest in Additional Training Breakdown by Experience**

**Table 5: Appropriate Providers for Future Trainings**

Answer	Count
NSGC	61
Scientific journal articles	60
Other professional organizational training	55
Drug manufacturers	45
Training through your workplace	35
FDA	28
A patient advocacy group	23
Word of mouth/discussions with colleagues	15
Other (please describe):	2
Popular media (TV, newspaper, magazines, etc.)	0
<b>Total</b>	<b>324</b>

**Table 6: Preferred Methods for Future Trainings**

<b>Answer</b>	<b>Count</b>
Seminar/lecture	76
Online training	53
Brochure/written literature	35
Workplace discussion	29
Sales pitch	1
Other (please describe):	1
<b>Total</b>	<b>195</b>

**Table 7: Participants Who Selected GCs as Appropriate Providers- Importance of Knowing About Therapies**

How important do you feel it is for GCs to know about available gene therapies for genetic conditions?	
<b>Answer</b>	<b>Count</b>
Extremely Important	32
Very Important	43
Moderately Important	14
Slightly Important	1
<b>Total</b>	<b>90</b>

**Table 8: Participants Who Selected GCs as Appropriate Providers- Other Providers Selected**

Which providers should feel comfortable discussing gene therapies with patients?	
<b>Answer</b>	<b>Count</b>
GC, Geneticist, Physician	75
GC, Geneticist	7
GC, Geneticist, Physician, Pediatrician or General Practitioner	6
GC, Geneticist, Other	1
GC, Physician	1

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